VOLUME 104 • OCTOBER 1959 • NUMBER 4

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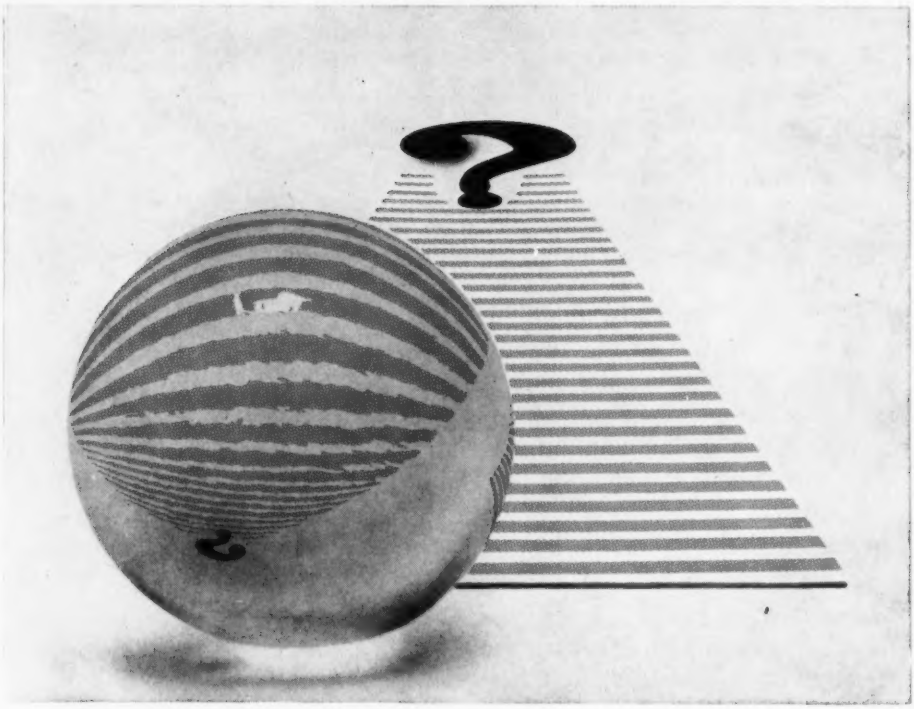

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References: 1. Dowling, H. F.: Postgrad. Med. 23:594 (June) 1958. 2. Gimble, A. I.; Shea, J. O., and Katz, S.: Antibiotics Annual 1955-1956. New York, Medical Encyclopedia Inc., 1956, p. 676. 3. Long, P. H., in Kneeland, Y., Jr., and Wortis, S. B.: Bull. New York Acad. Med. 33:552 (Aug.) 1957. 4. Rein, C. R.; Lewis, L. A., and Dick, L. A.: Antibiotic Med. & Clin. Ther. 4:771 (Dec.) 1957. 5. Stone, M. L., and Mersheimer, W. L.: Antibiotics Annual 1955-1956, New York, Medical Encyclopedia Inc., 1956, p. 862. 6. Campbell, E. A.; Prigot, A., and Dorsey, G. M.: Antibiotic Med. & Clin. Ther. 4:817 (Dec.) 1957. 7. Chamberlain, C.; Burros, H. M., and Borromeo, V.: Antibiotic Med. & Clin. Ther. 5:521 (Aug.) 1958. 8. Prom, F., and Alli, J. H.: Antibiotic Med. & Clin. Ther. 5:539 (Nov.) 1958.

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2. Current personal communications; in the files of Wallace Laboratories.
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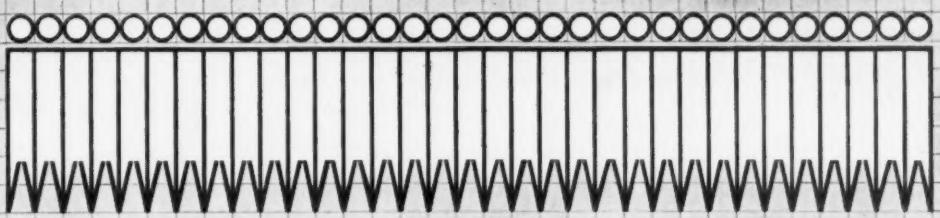

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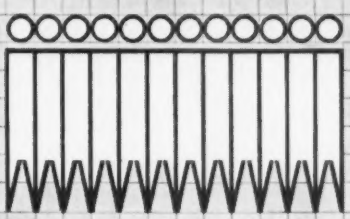

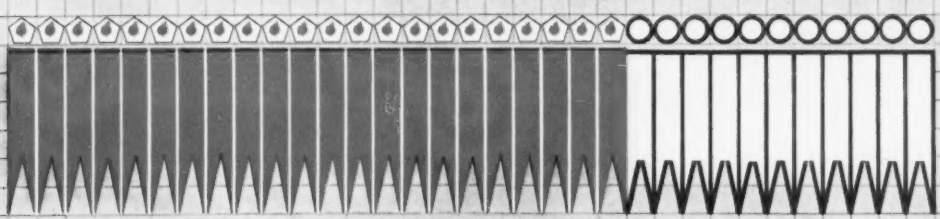

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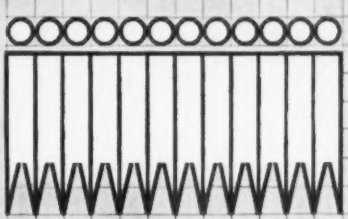

1. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.
2. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.

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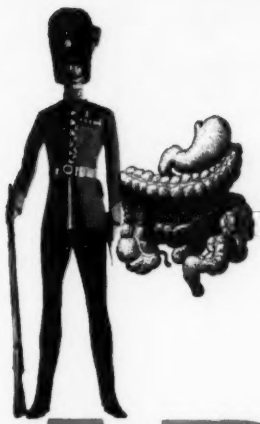

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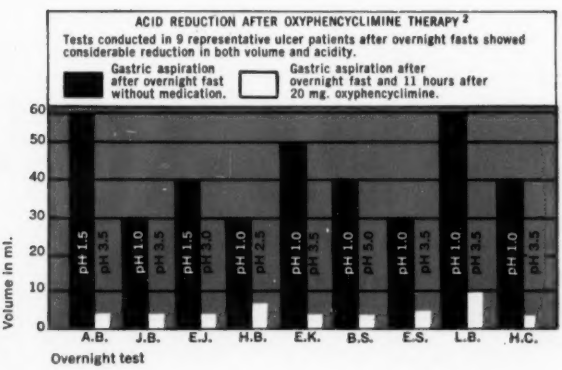

References: 1. Steigmann, F.: Study conducted at Cook County Hospital, Chicago, Illinois: In press. 2. Winkelstein, A.: Am. J. Gastroenterol. 32:66 (July) 1959. 3. Data in Roerig Medical Department files. 4. Leming, B. H., Jr.: Clin. Med. 6:423 (Mar.) 1959.

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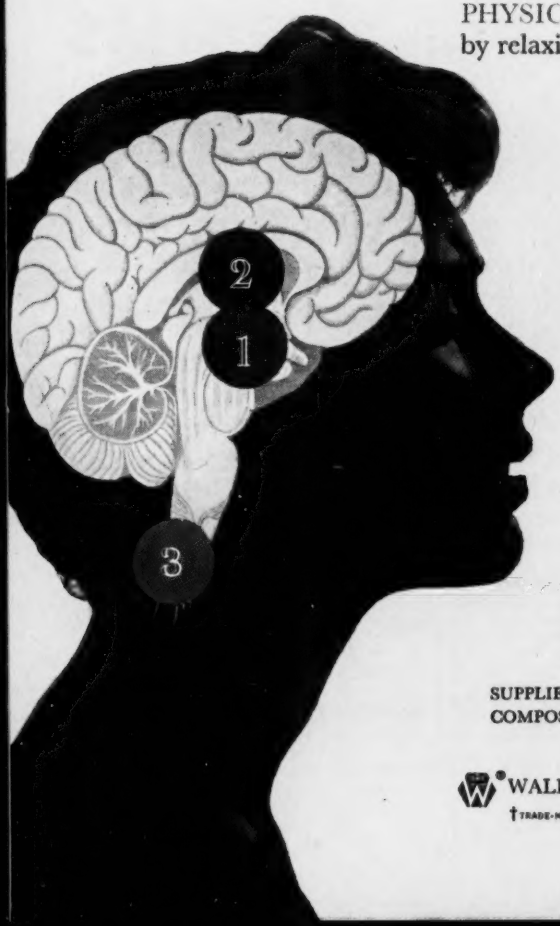

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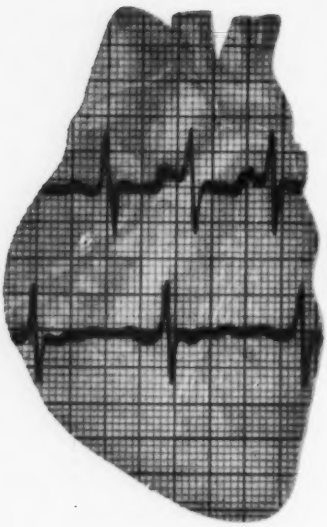

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1. Smith, J. M.: Lederle Bull. Symposium Report, 1:1, 1958.
2. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Internal Med. 100:750, 1957.

* U. S. Patent 2,895,881

REFER TO PDR PAGE 867

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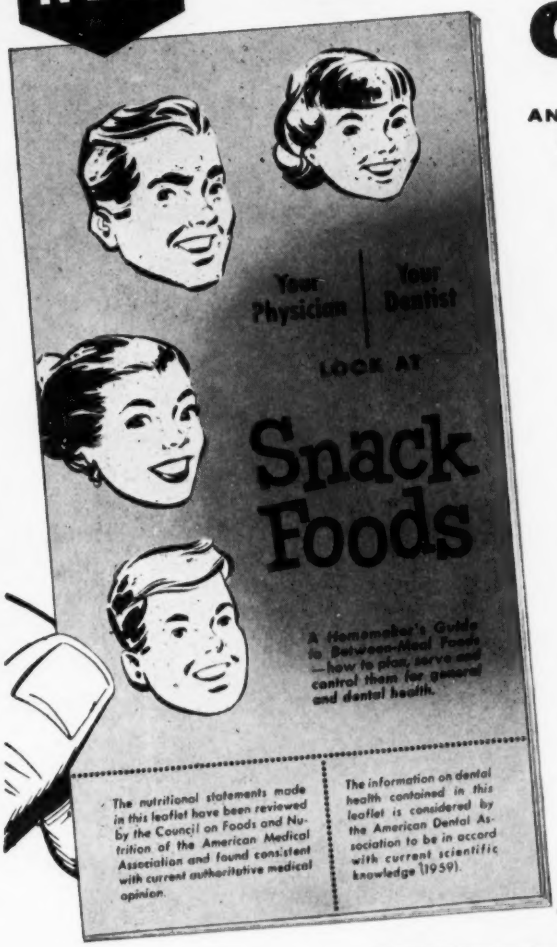
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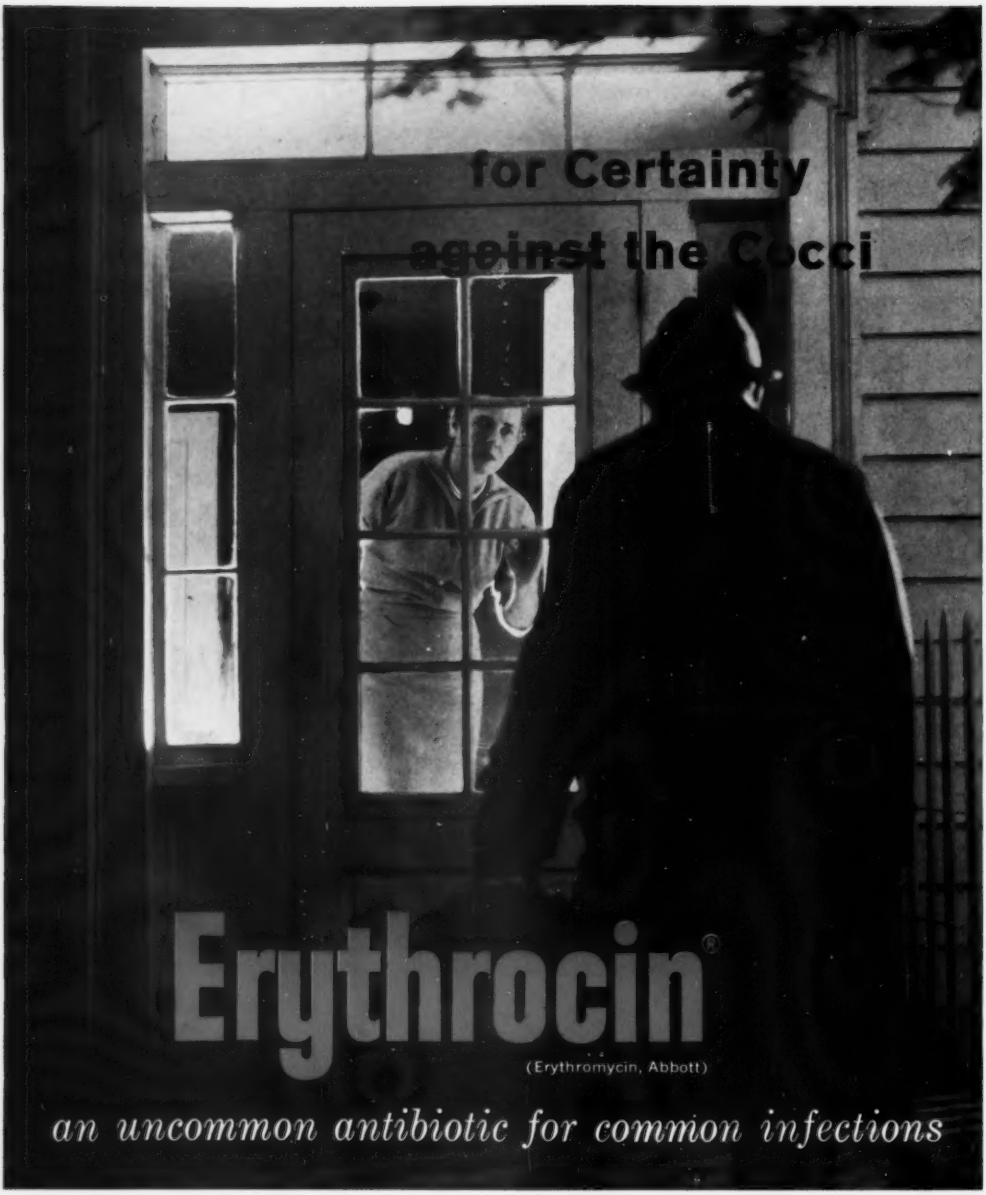

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Editorials

Hepatic Coma

Thoughts on Terminology

For many years, coma—often prolonged—has been described as a common prelude to the death of patients with liver disease. This altered state of consciousness has been known as hepatic coma (probably a better term than "liver coma," which presumes a prior conscious state for the organ). The pathogenesis was little understood, nor was it investigated until Adams, Foley, and their colleagues,[1,2] by careful neurological study of patients, provided a clinical description of the syndrome in all its stages and made it possible to detect the early signs of the condition. This advance has awakened interest in investigation of the relationship of ammonia to the syndrome, already suggested by Kirk,[3] van Caulaert,[4] Fuld,[5] and others. The results have been a multitude of studies and papers on the subject (as could have been expected) and a welter of terms for the syndrome. The purpose here is to view critically some of these terms with consideration of present knowledge.

"Cholemia," literally "bile in the blood" (from the Greek chole-, bile, plus -emia, in the blood) implies an excess of bile constituents in the blood, presumably bilirubin in particular. Hepatic coma frequently occurs in the absence of jaundice, however, and hypercholesterolemia is certainly not of regular occurrence—to name two important bile constituents. This term should be abandoned until a syndrome due to bile in the blood is described. (Hippocrates apparently knew of one, calling it "madness on account of bile" [Davidson and Summerskill [6]].)

"Liver failure" is not a good alternate term for hepatic coma, because it implies progressive impairment of liver function by disease. Yet, hepatic coma is common in chronic liver disease as well as in active progressive disease. Moreover, liver failure may prove fatal without any sign of hepatic coma.

Another term which now has been linked to hepatic coma is "meat intoxication" or, better, "protein intoxication." The suggestion here is that some substance(s) in protein is released in the intestine, bypasses the diseased liver owing to portal-systemic shunts, and "intoxicates" the body, especially the brain. Animal studies over many generations and, more recently, studies in man substantiate this and presumably form the basis for modern treatment with oral antibiotics.[7] These latter are thought to prevent bacterial breakdown of protein or amino acids to whatever substance or substances had been intoxicating the body. "Portal-systemic encephalopathy" [8] was devised to describe the neurologic result of this deviation from the liver to the brain of "toxin"-laden blood. Not

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by any means are all instances of hepatic coma due, as far as we can tell, to this syndrome. More will be said of other causes later. Meanwhile, both the terms, "protein intoxication" and "portal-systemic encephalopathy," appear to be in good order when they are used for what they actually mean and not as a synonym for hepatic coma.

It may be useful to inquire concerning the toxins themselves. Ammonia (or ammonium, depending upon the state of ionization) is now most popular. Hence, the term "ammoniagenic coma." It is true that the syndrome can be reproduced in susceptible patients with liver disease by both oral and intravenous ammonium salts with an associated rise in the blood ammonia concentration. In this circumstance, "ammoniagenic coma" seems suitable. Protein feeding in these patients also results in hyperammoniemia, but this analogy is not sufficient proof that ammonia is the only, or even the most important, poison in other circumstances. One important reason for the present attraction of ammonia is the relative ease of its determination in the blood (e. g., the simple procedure of Conway). Amines can be measured with some difficulty, but the relative concentration of the various amines and their relative toxicity are unknown. Other products of intestinal bacterial action or of digestion have been little studied but may be as important as ammonia, or more so. Until the influence of other poisons is eliminated, the term "ammoniagenic coma" should be reserved for coma resulting from the administration of ammonium salts. "Hepatocerebral intoxication," although denoting the two organs most importantly concerned, has little more to recommend its use, as the toxin is undefined and no further definition of the syndrome is made.

Hepatic coma may be precipitated not only by ammonium salts and by protein but also in many other circumstances, e. g., injudicious use of hypnotics and sedatives after major operations, when severe hyponatremia, water intoxication, or hypokalemia occur, and by diuretics such as acetoazolomide and chlorothiazide. Whether any or all of these is related to ammonia metabolism is unknown. The difficulty in terminology is evident.

After surveying the various terms, the widely used, well understood, and descriptive "hepatic coma" still seems best. It is not without its difficulties and incongruities, however. Most important, it leaves no room for the early stages or for the frequent episodic nature ("episodic stupor" of McDermott and Adams[9]). In spite of these and other arguments against it, the term probably will remain for some time to come.

We may then use the term "hepatic coma" to mean all stages of the altered state of consciousness in liver disease, usually with the characteristic, but not specific, "flapping" tremor and with the frequent electroencephalographic changes. We might append certain qualifying words, such as "ammoniagenic," "due to protein intoxication," "associated with hyponatremia," and "hypokalemia," when any one applies.

The stages of hepatic coma might be defined as follows: (1) the stage of mild or marked confusion, sometimes with excitement, euphoria, or depression, and often with prolonged sleep or drowsiness; (2) the stage of stupor, but with the patient still arousable and usually greatly confused; (3) the stage of true coma. A combination of the first two stages has been called "impending hepatic

coma," an unwieldly combination implying that coma always ensues, which is not true. "Pre-coma" is easier to handle and, although not entirely free from the above implication, seems better.

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Thorndike Memorial Laboratory
Boston City Hospital
Boston 18

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Obstructive Emphysema in Cigarette Smokers

ARNOLD L. FLICK, M.D., and RICHARD R. PATON, M.D., Seattle

All of the patients we have seen with idiopathic obstructive emphysema have given a history of many years of cigarette smoking. This observation has been strengthened by published reports [1-3] relating emphysema and smoking. Other articles relate bronchitis [4-7] and wheezing attacks ("smoker's respiratory syndrome") [8] to smoking, and it is apparent from the respective definitions that emphysema is included in these studies. Smokers also suffer higher death rates from noncancerous pulmonary disease than do nonsmokers.[9]

In a search for a consistent definition for emphysema, we have found none better than Laennec's original observation [10]:

> The general signs of this malady are somewhat uncertain; dyspnea is the chief characteristic and it is one of those varieties which we confuse under the name of asthma . . . all of the patients in whom I have discovered this affection were subject to habitual cough. I have met with patients who have declared that they had neither habitual cough nor expectoration, but after observing them carefully I have found they were also subject to slight coughing and that every morning they expectorated a little viscid bronchial matter. . . . The malady . . . may last during a very great number of years and does not always prevent the sufferer attaining a fairly advanced age.

We define obstructive emphysema by the presence of signs of lower respiratory obstruction in a patient who has not had juvenile or adolescent asthma, who does not have pneumoconiosis, and who does not have more than minimal inactive granulomatous lung disease. This definition will include many persons without disability but who have had intermittent attacks of "asthma" which first appeared in their fourth or later decade; it will include those without significant disability but who wheeze on exertion and those with typical idiopathic obstructive emphysema, but not normal elderly persons with benign increased residual pulmonary volume.[11]

Emphysema, as so defined, is common. In an effort to delineate further its relationship to smoking, we have studied 222 patients at the Seattle Veterans Administration Hospital. This article summarizes our observations.

Methods

We examined 222 male patients between August and November, 1958. A detailed history regarding smoking habits and lower respiratory symptoms, a physical examination, and maximum expiratory flow rates (MEF) were obtained.

Selection of Patients.—With the following exceptions, all male patients on a ward at a given time were examined, and only patients examined in this manner are included in this study. No one was excluded on the basis of "intrinsic asthma." Specifically excluded were patients with the following conditions:

(1) History of asthma dating from childhood or adolescence (five patients).
(2) Past history of thoracotomy (approximately 10 patients).
(3) Stopped smoking prior to this study (approximately 20 patients).
(4) Fever in the preceding 48 hours. (These patients were later studied when afebrile.)
(5) Congestive heart failure manifested by pulmonary rales or pedal edema.
(6) Advanced granulomatous lung disease.
(7) Illness so severe that the patient could not perform the MEF measure unassisted (approximately 100 patients).

Submitted for publication Jan. 6, 1959.

From the Medical Service of the Seattle Veterans Administration Hospital and the Department of Medicine, University of Washington School of Medicine. Resident in Medicine, Seattle Veterans Administration Hospital and the University of Washington, now trainee of the National Institute of Arthritis and Metabolic Diseases in gastroenterology at the University of Washington (Dr. Flick); Resident and Assistant in Medicine, Seattle Veterans Administration and the University of Washington, now Clinical Investigator, Veterans Administration, Seattle Veterans Administration Hospital (Dr. Paton).

(8) Pain (e. g., recent surgery) preventing maximal respiratory effort (approximately 50 patients).

In addition, after the first 100 patients were obtained, men under 40 years of age were not studied.

The majority of patients included in this study were ambulatory patients awaiting elective surgery, convalescing from various diseases, undergoing diagnostic evaluations, or receiving active therapy for medical or psychiatric illness. We are not aware of bias in the selection of these patients.

Smoking History.—Patients were questioned in detail with regard to (*a*) whether they smoke, (*b*) what they smoke, (*c*) the age when they began smoking habitually, (*d*) the average number of cigarettes, cigars, or pipefuls of tobacco smoked per day over the years they had smoked. For those smoking cigarettes this information was converted to "pack years" of smoking, by means of the following formula:

$$\text{"pack yr."} = \frac{\text{yr. smoking} \times \text{no. cigarettes/day}}{20}$$

The number of "pack years" so obtained is considered an estimate, since there is no way of evaluating the reliability of the smoking history, particularly the average number of cigarettes smoked per day over a lifetime of smoking.

Cigarette butts from the patient's ash tray were measured and recorded in most cases.

History of Respiratory Symptoms.—All patients were questioned regarding the presence or absence of cough, sputum, or "colds settling in the chest or lungs." No details were solicited, and the answers were tabulated only as "yes," "no," or "indeterminant."

Maximal Expiratory Flow Rate.—The MEF was obtained by the "Puffmeter," designed by Goldsmith and Young,[12,13] which directly measures the peak flow rate in liters per minute. This is a simple and reliable portable instrument giving reproducible results. The patient was studied in the sitting position, holding the mouthpiece himself. His nose was occluded. Each patient was encouraged to obtain a maximal reading on the "Puffmeter," and the best single reading of 5 or 10 tries was recorded. In all instances there were at least three values agreeing within 15 liters per minute.

Results

In our data "Smokers" refers to cigarette smokers only; pipe and cigar smokers are classified with "Nonsmokers."

Figures 1 and 2 relate the patient's age to MEF. Figure 1 is a scattergram of all patients; Figure 2 is a plot of the same data, showing average MEF for age groups

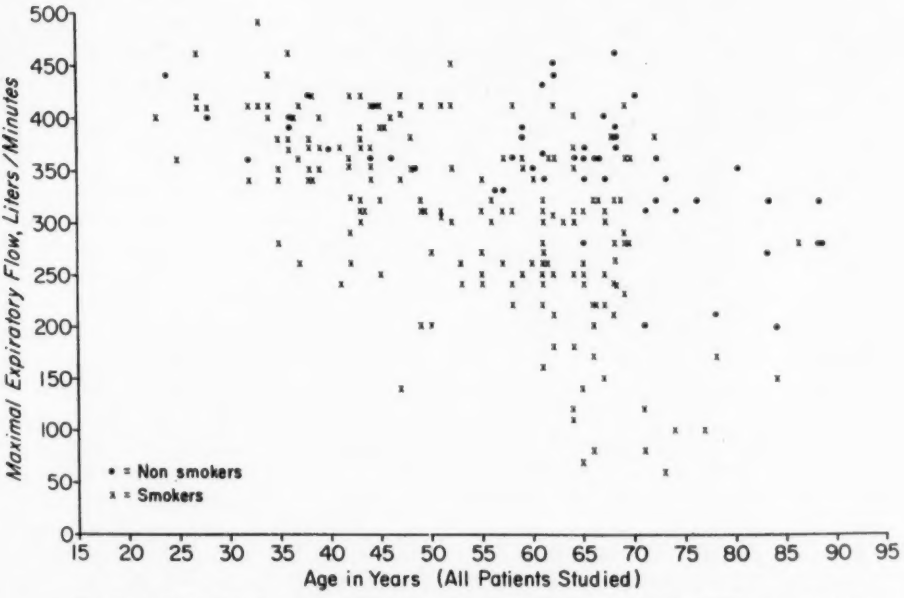

Fig. 1.—Relationship between MEF rate and age. A distinct decline in MEF among some smokers is seen to begin at about 40 years of age and to progress thereafter. Among nonsmokers, no apparent change is noted until 70 years.

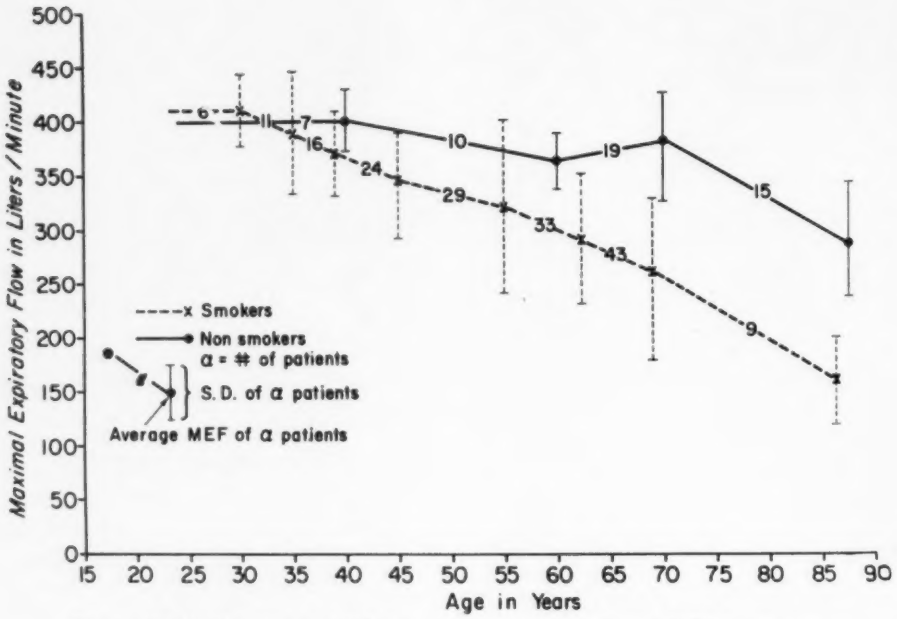

Fig. 2.—Relationship between MEF rate and age. Average values of MEF for age groups, with accompanying standard deviations, are plotted for smoking and nonsmoking groups. At 60 to 70 years the difference is significant to $P<<0.001$.

of smokers and nonsmokers. Standard deviation for each point is superimposed on Figure 2. The data show no appreciable change in MEF for nonsmokers up to age 70 years; thereafter, the MEF declines. This late decline may be attributable to feebleness and diseases of age rather than to known pulmonary disease. In contrast, smokers show loss of MEF beginning in their mid-30's, and this loss is progressive with age. Note that the range of values in smokers is greater than in nonsmokers, suggesting the variable effect of smoking in different persons.

Between ages 60 and 70 years there are 20 nonsmokers and 61 smokers (Fig. 1). The mean MEF's are 378 and 258 (standard deviations 42 and 72, respectively). This difference is highly significant ($P<<0.001$).

Figures 3 and 4 are graphs of data relating MEF to "pack years" for patients under 70 years of age. Figure 4 includes a standard deviation about the means of groups plotted from the scattergram of Figure 3. Age is ignored as a factor in these graphs, since it is already shown that to age 70 years nonsmokers do not have significant loss of MEF (Fig. 2). Furthermore, the nonsmokers have a slightly older age distribution (insert, Fig. 3), and so any age bias would favor the smokers.

Figure 4 shows a general decrease in MEF with increase in "pack years," the dip at 50 "pack years" being unexplained. This decrease may be seen to begin between 30 and 40 "pack years," which usually corresponds to 45 or 55 years of age. It is interesting that the only nonsmoker below 330 liters per minute MEF was extremely obese and had recently recovered from congestive heart failure.

Figure 5 compares the MEF of smokers with cigarette-butt length of 30 mm. or greater to smokers leaving butts of less than 30 mm. It is noted that those smoking less of their cigarettes have a higher mean MEF.

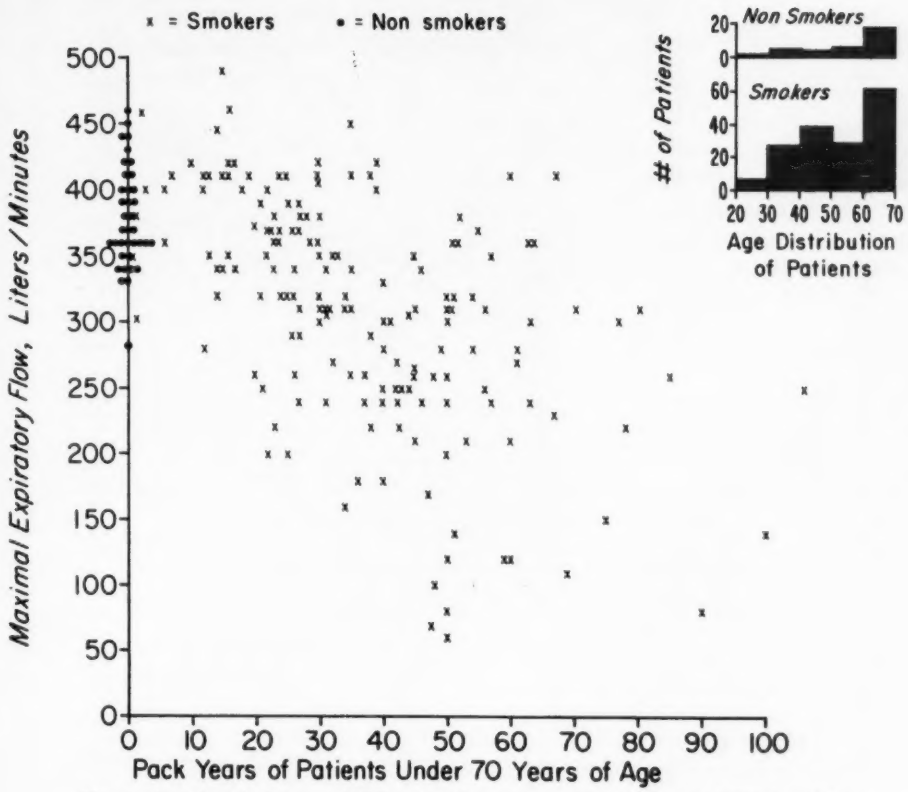
x = Smokers
• = Non smokers
Maximal Expiratory Flow, Liters / Minutes
Pack Years of Patients Under 70 Years of Age
# of Patients
Non Smokers
Smokers
Age Distribution of Patients

Fig. 3.—Relationship between MEF rate and "pack years." A decline in MEF is noted as the "pack years" increase, beginning after 25 "pack years." The age distribution of the persons concerned is summarized in the graphic insert; it may be noted that the nonsmokers are proportionately older than the smokers.

Above 35 "pack years" there are 21 patients in the group leaving long butts and 64 in the group leaving short butts, with similar mean "pack years" of 51 and 53. Respective mean MEF's are 315 and 250 (standard deviations 71 and 84), this being significant to $P<0.002$.

Tables 1 and 2 are compilations of replies to questions regarding habitual cough, habitual raising of sputum, and "colds settling in the chest." Smokers replied positively to all three categories more often than did nonsmokers. That there were more patients with sputum than with cough is perhaps explained by nasal discharges or the raising of early morning sputum without a conscious coughing effort.

Comment

The above data, showing a relationship between expiratory obstruction and smoking, admit of only three explanations: (1) bias in the series, making apparent relationships meaningless; (2) an unknown etiologic factor which parallels smoking habits, making the above apparent relationship coincidental, and (3) expiratory obstruction being etiologically related to cigarette smoking.

As to the first, we know of no bias in the selection of the series here reported, but studies on different population groups are needed for confirmation and extension of our data.

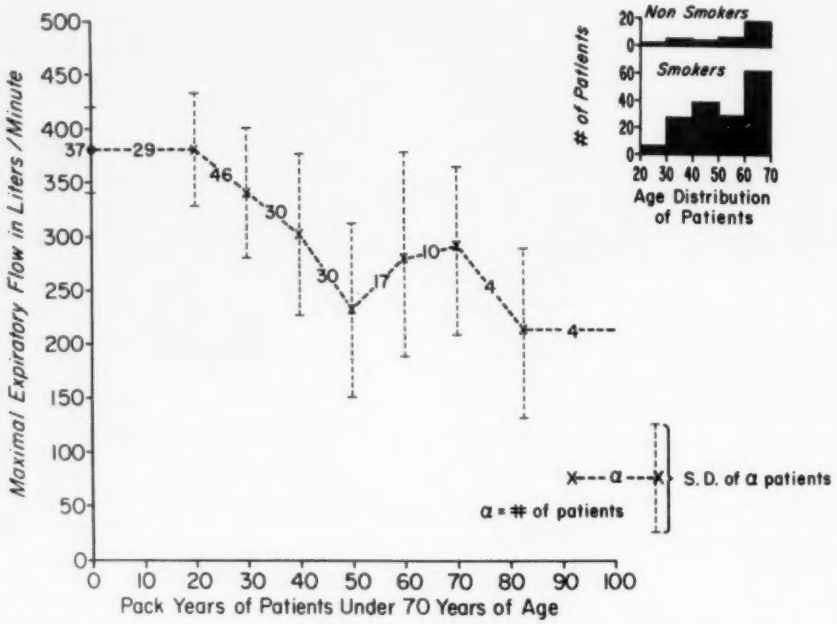
Maximal Expiratory Flow in Liters / Minute
Pack Years of Patients Under 70 Years of Age
Non Smokers
Smokers
# of Patients
Age Distribution of Patients
S. D. of α patients
α = # of patients

Fig. 4.—Relationship between MEF rate and "pack years." Average values of MEF for groups with similar "pack years" exposure are plotted, with accompanying standard deviations. Nonsmokers are plotted as 0 "pack years."

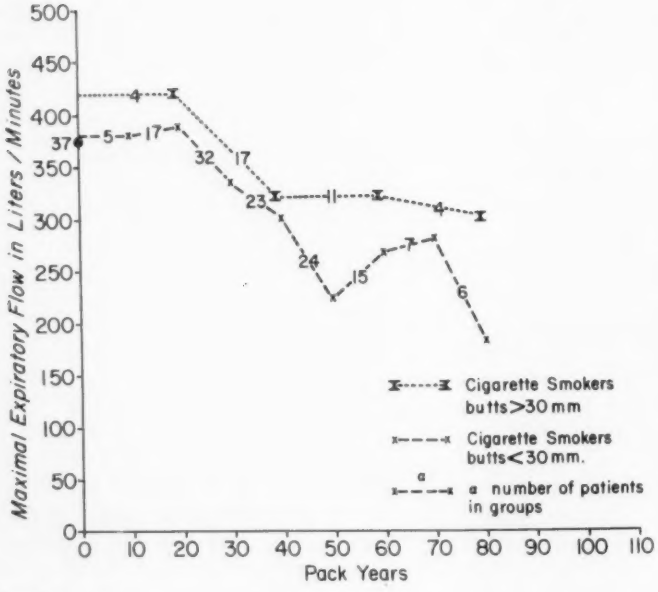
Maximal Expiratory Flow in Liters / Minutes
Pack Years
Cigarette Smokers butts>30 mm
Cigarette Smokers butts<30 mm.
α number of patients in groups

Fig. 5.—Relationship between MEF rate and "pack years" for persons who leave cigarette butts of length greater than 30 mm. and less than 30 mm. Above 35 "pack years" this difference is significant to $P<0.002$.

TABLE 1.—*Actual Number of Patients on Whom Tabulations Were Done*

	Cough		Sputum		Chest Cold	
	Yes	No	Yes	No	Yes	No
Smokers	83	74	103	53	83	55
Nonsmokers	5	46	13	36	15	32

TABLE 2.—*Per Cent of Patients Answering "Yes" to the Questions*

	With Cough	With Sputum	With Chest Cold
Smokers	55	65	60
Nonsmokers	10	25	30

Regarding the second possibility, Heath's prospective study[14] describes apparently minor personality differences between smokers and nonsmokers, but he does not consider the possible influence of military service in introducing the smoking habit.

We feel that the data presented point to the third possibility as the proper conclusion: Cigarette smoking is an essential factor in the pathogenesis of "idiopathic" obstructive emphysema. In support of this contention, a brief review of the pathogenesis of emphysema and of studies on the effects of smoking follows.

Laennec's[10] concept of emphysema has been altered in detail and extended, but the essentials are applicable to present theory:

> We can give a kind of mechanical explanation for emphysema. It may be conceived that the mucous secreted in the bronchi must, especially if it is highly viscid, offer great resistance to the free passage of air on inspiration and expiration. . . . Now, the muscles by which inspiration is performed are strong and numerous, while on the contrary, expiration is brought about solely by the elasticity of the parts and the weak contraction of the intercostal muscles; it must therefore happen that the air having overcome the resistance offered to it by mucous during inspiration, is unable to force its way back through the same mucous, and remains as it were imprisoned. . . . The subsequent acts of inspiration, bringing fresh quantities of air to the same place, inevitably cause dilation of the air cell. . . .

More recently, terminal respiratory bronchiolitis with surrounding centrilobular emphysema has been described as the earliest specific histologic lesion.[15,16] Loss of the elastic properties of the alveoli has also been suggested as the earliest lesion.[17,18] However, this might rather be considered as a consequence of terminal bronchiolitis, since (1) centrilobular emphysema is described pathologically following terminal bronchiolitis,[15,16] (2) bronchiolar obstruction during forced expiration does not necessarily depend upon loss of alveolar elasticity but may be consequent to inflammatory obstruction and weakening of the bronchiolar wall, (3) measurements showing decreased compliance (loss of elasticity) were made in advanced cases of emphysema,[19-21] where primary pathologic changes are accompanied by secondary ones. In summary, although alveolar distention, rupture, and fibrosis are important in the evolution of the disease, these changes are not necessarily primary.

Terminal bronchiolitis, then, is sufficient to determine all the pathophysiologic abnormalities of emphysema. The inflamed and partially obstructed bronchioles lead to the distention and rupture of alveoli. This obstruction also leads to infection and increased secretions, apparent as bronchitis and cough. Cough, with its attendant increases in intrathoracic pressure, aggravates the obstruction of the inflamed terminal bronchioles.[17] Finally, loss of parenchymal elasticity leads to further bronchiolar obstruction and infection (Fig. 6). This sequence of events is in general agreement with views of others.[2,18,22]

The frequent coexistence of bronchitis and emphysema has been noted elsewhere.[2] Bronchitis aggravates the emphysema in the manner described above (Fig. 6) and also by interference with drainage of infected secretions from the terminal bronchioles. This might be particularly true with the abnormal bronchial epithelium of cigarette smokers,[23,24] where the normal mucosa is altered by a proliferation of goblet cells, squamous-cell metaplasia, basal-cell hyperplasia, alterations in the density and ap-

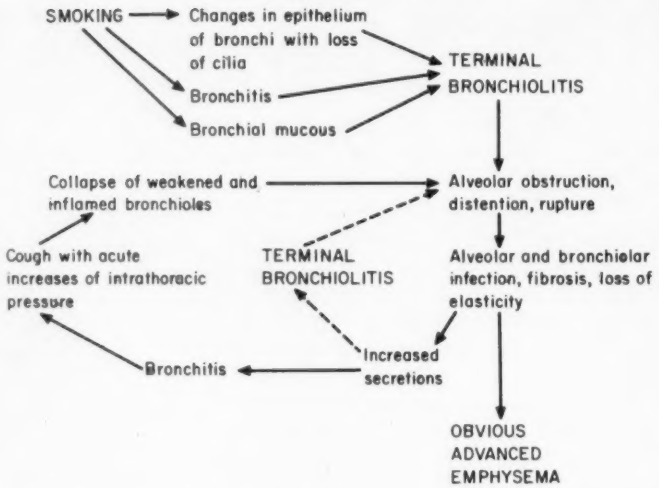

Fig. 6. — The vicious circle of "smoker's emphysema." This formulation is intended to show that after a point the disease may become self-perpetuating even if the person discontinues smoking.

pearance of the cilia, and the appearance of "islands" of nonciliated atypical epithelium. The effect of these abnormalities on the drainage of mucus from the terminal bronchioles may be inferred from the observations of Hilding,[25] who emphasized the importance of a normal ciliary cover for proximal movement of the "mucous stream" and showed that "islands" of nonciliated epithelium were marked by mucous stasis.

It remains to be shown that cigarette smoke causes terminal bronchiolitis as well as the epithelial changes outlined above. Clough has commented on the inhaled particle size in this regard.[6] Whereas dusts of larger caliber settle more rapidly and tend to be removed within the nasal passage and large bronchi, cigarette smoke reaches the terminal bronchioles and alveoli themselves, producing direct local irritation. In this regard, one may recall that cigarette smoke is inhaled orally, thus bypassing the filtering of the nasal passages. Further, acute expiratory obstruction has been shown to follow inhalation of cigarette smoke in both man [20] and the guinea pig.[26]

The final demonstration of cigarette smoke as the cause of emphysema, however, must rest on clinical rather than experimental studies. Lowell [1] and Phillips [2] together reported 72 unselected cases of emphysema, all of whom smoked. Oswald's [4] definition of Grade 4 and Grade 5 bronchitis obviously includes the emphysematous; he noted a strong correlation between smoking and "bronchitis." Greene and Berkowitz,[5] in their demonstration of the relation of smoking and bronchitis, would also have included anyone with emphysema among those with bronchitis. Similarly, Hammond and Horn, in studying various diseases and smoking habits,[9] include the emphysematous among their group of noncancerous pulmonary diseases. They found the risk of death from diseases in this category to be 2.85 times greater in smokers than in nonsmokers, no other single category of diseases showing an increased risk of this magnitude.

The above-mentioned reports [1,5,7,9] have also examined the quantitative aspects of smoking in relation to lung disease. Without exception, these show that the heavier smokers have more symptoms and higher death rates. On the other hand, cigar and pipe smokers, who generally do not inhale, show fewer symptoms [5,7] and for that matter have less bronchogenic carcinoma.[9,27] Our observations are similar and form the basis for the grouping of cigar and pipe smokers with "nonsmokers."

Our own data agree with and extend the observations already cited. They indicate that there is a spectrum of loss in the ease of expiration (measured by decreased MEF), which becomes apparent in smokers after some 30 years of smoking and progresses with increased smoking. Further, it shows a great individual variation among smokers: many have negligible loss; others have moderate loss, which is regarded by them as sufficient only to give pause before undertaking strenuous exercise, while in a last small group of smokers this loss deserves the designation of severe disease with disability and often death as a result.

Differences in smoking habits are a likely cause of variation in individual response to smoking. Hilding has commented on the difficulty in quantitating smoking, having found that the time of inhalation per cigarette varies from 6 to 35 seconds among smokers [28] and that the longer the smoke is held in the lungs the more particulate matter is retained.[25] However, we have shown a crude correlation between heavier smoking habits and emphysema (Fig. 4). We have also measured cigarette-butt lengths, believing that this is a further quantitation of smoking and perhaps also measures a filtration function. Figure 5 shows a higher MEF in smokers who leave cigarette butts over 30 mm. long than in those who leave butts less than 30 mm. long. This difference is highly significant ($P<0.002$) above 35 "pack years" (see Results).

In marked contrast to this finding of extensive and fairly generalized decrease of MEF among smokers, no single instance of such loss was noted in nonsmokers up to age 70, and poor function beyond this age was apparently attributable to feebleness rather than lung disease. Cigar and pipe smokers under 70 years were similar to nonsmokers in this regard, and they are included in the category of nonsmokers.

There are no data disputing this view of cigarette smoking as a cause of emphysema. Although Mayer and Rappaport [29] questioned the relation between chronic bronchitis and emphysema, they agreed on the invariable presence of bronchiolitis. Attinger et al.[21] concluded there is no difference in maximal breathing capacity between smokers and nonsmokers. Despite their conclusion, examination of their work shows, with one exception, all of their subjects to be under 40 years of age, this being generally below the age of significant decline in MEF (Fig. 1). Even so, the average maximal breathing capacity of their nonsmokers was 156 liters per minute, whereas that of their smokers was 135 liters per minute. Furthermore, the only man in their study over 40 years of age, a smoker of 55, had a maximal breathing capacity of 84 liters per minute, the lowest in the series.

Emphysema is a common disease. It is frequently disabling, having marked social and economic effects. In England it causes more deaths than lung cancer or pneumonia.[22] The material presented here and elsewhere warrants attention to cigarette smoking as the cause of "idiopathic" obstructive emphysema.

Summary

Data are presented on the smoking habits and the maximal expiratory flow rates (MEF) of 222 male patients at the Seattle Veterans Administration Hospital. The MEF was selected as the best single screening test for emphysema.

Nonsmoking men show minimal change in MEF to age 70. Many smokers show moderate to marked decline in MEF with increasing age.

Heavy smokers show more loss in MEF than do light smokers.

Smokers who leave short cigarette butts show more loss in MEF than those who leave longer butts.

Habitual cough, habitual raising of sputum, and "chest colds" are commoner in smokers than in nonsmokers.

The pathogenesis of emphysema is briefly reviewed and discussed, with emphasis on the terminal bronchiolitis as the primary lesion.

Evidence indicating cigarette smoking as the likely cause of "diffuse hypertrophic idiopathic emphysema" is presented.

Dr. Robert S. Evans and Dr. Paul P. Van Arsdel Jr. gave helpful criticism of this manuscript.

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Inhibition of Cholesterol Synthesis with the Use of Mer-29

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Although the relationship between serum cholesterol and the pathogenesis of atherosclerosis has not been definitely established, it has been widely investigated. The bulk of the evidence favors an etiologic association between hypercholesteremia and atherosclerosis; both may be the end-products of an altered metabolic state. Because of this possibility, many therapeutic attempts have been made to lower serum cholesterol.

The serum cholesterol concentration in normal persons is approximately 37% of the total lipid content of the blood.[1] The range is 190 to 250 mg. per 100 ml. of serum. Approximately 30% of the total cholesterol is in the free state and 70% in the form of cholesterol esters.[2] The biosynthesis of cholesterol from acetate[3] is thought to proceed as indicated in Figure 1.

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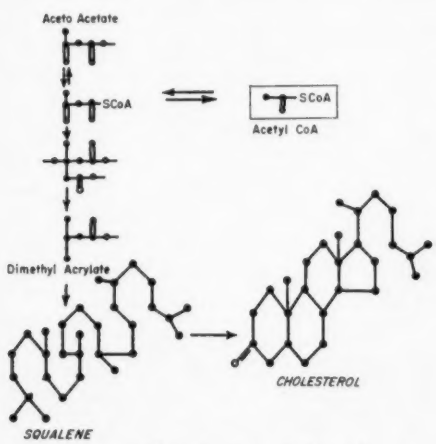

Fig. 1.—Biosynthesis of cholesterol.

Acetyl coenzyme A (CoA) condenses to form acetoacetyl CoA, which with the addition of one more acetyl CoA and a decarboxylation produces dimethylacrylate, which is a five-carbon unit. There follows a condensation of six of these units through various steps to form the long-chain hydrocarbon squalene. The squalene cyclizes and forms cholesterol by losing three methyl groups.

The study of cholesterol biosynthesis is facilitated by the use of radioactive C^{14} acetate.[4] These studies indicate that the injected acetate is rapidly converted to liver cholesterol and in a period of a few hours the free cholesterol in the liver is in equilibrium with the plasma free cholesterol. Studies by Keys and others[5-9] indicate that the dietary cholesterol has a minimal effect on serum cholesterol concentration. In these studies in normal persons, the serum cholesterol increased with a concomitant increase in the amount of fat in the diet, but there was little effect from an increase in dietary cholesterol alone. In response to reduction of fat content of the diet, there was a sharp decline in the serum cholesterol in the first 7 to 10 days, which fell to 65% to 70% of control values in three weeks. The serum cholesterol then remained at this level for six to nine months, at which time it rose to the predietary level. This was considered to be due to the gradual replacement of exogenous cholesterol by endogenous cholesterol synthesis.[10,11] It is postulated that the liver maintains a balance between exogenous and endogenous cholesterol, such that the serum concentration is held relatively constant in normal persons.

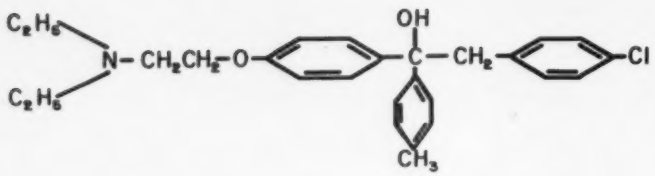

Fig. 2.—Structural formula of Mer-29.

In an attempt to produce a depression of the serum cholesterol, three basic methods have been tried. They are attempts to (1) diminish cholesterol absorption from the gastrointestinal tract, (2) increase the metabolic process and biliary excretion of cholesterol, and (3) inhibit the endogenous liver synthesis of cholesterol. It is with the latter mechanism that this paper is primarily concerned, with the use of the compound designated as Mer-29, a synthetic compound whose structure in seen in Figure 2. A preliminary clinical report has been made by us.[12] The specific mechanism of action of Mer-29 is not known, but one effect is to inhibit cholesterol synthesis in the liver.[13,14] This was demonstrated in rats with the use of intraperitoneal C^{14} sodium acetate, the natural precursor of endogenously synthesized cholesterol. After the use of Mer-29 for seven days, the liver of killed rats showed 85% inhibition of cholesterol synthesis as compared to the control group.[13,14] These results in themselves justified a clinical evaluation of this compound.

Methods and Materials

Forty-one patients with a serum cholesterol of more than 250 mg. % were studied, but only thirty-six patients continued to take the drug for four weeks or more. The serum cholesterol determinations were done by the same technician, with the use of the same colorimetric method. A baseline serum cholesterol was obtained on each subject prior to the institution of therapy with the use of an average of at least two cholesterol determinations. The subjects involved in the study were under no specific dietary restriction. The dosage of Mer-29 varied from 100 mg. to 1,000 mg. for periods ranging up to 15 weeks. The serum cholesterol levels were determined at weekly or biweekly intervals.

Concurrent laboratory observations were made for evidence of hepatic and renal toxicity. Liver-function determinations, complete blood cell counts, and urinalyses were done on all patients prior to drug administration. These were repeated when indicated.

TABLE 1.—*Statistical Analysis* *

Daily Dose, Mg.	Control Level, Mg. %	Change from Control Level to 1 Wk., Mg. %	2 Wk., Mg. %	4 Wk., Mg. %
250	325 (11) ±47	−38 (7) ±28	−48 (9) ±51	−69 (8) ±24
500	323 (13) ±64	−25 (9) ±55	−41 (7) ±41	−53 (13) ±65
1,000	300 (17) ±42	−41 (14) ±58	−61 (10) ±50	−57 (15) ±50
All subjects	314 (41) ±51	−35 (30) ±51	−51 (26) ±47	−58 (36) ±51

* Analysis of the effect of Mer-29 on cholesterol concentration in the serum, with use of different doses of the drug. Numbers in parentheses indicate number of patients. Figures represent arithmetic mean ± 1 standard deviation.

Results

The results in the 36 subjects treated with Mer-29 for four weeks or more are summarized in Table 1. The subjects were divided into three dosage groups. The dosages were 250 mg., 500 mg., and 1,000 mg. per day. The mean changes in milligrams per cent from control levels are noted at one, two, and four weeks, respectively. The number of patients are listed in each dosage period, and 1 standard mean deviation is likewise noted. All the control levels are shown irregardless of completion of this study by the patients involved. The changes from controls were determined by the difference between the cholesterol level of each patient at the stated interval and his own control level.

Eleven subjects who received a dose of 250 mg. per day were studied. The mean serum cholesterol concentration progressively decreased to a maximum reduction of 69 mg. % after four weeks of therapy.

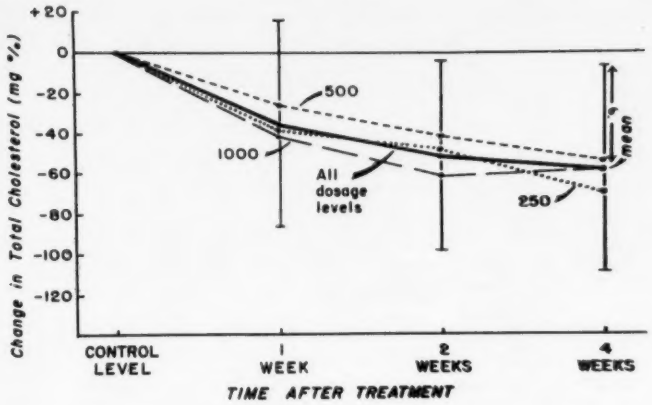

Fig. 3.—Graphic summary of effect of Mer-29 on the serum cholesterol concentration, giving 250, 500 and 1,000 mg. of the drug per day. The heavy line is the mean for all doses.

Thirteen subjects received 500 mg. per day. A depression in the serum cholesterol was noted within one week and continued to a maximum reduction of 53 mg. % after four weeks of therapy.

Seventeen patients received 1,000 mg. per day. At the conclusion of one week of treatment, the average serum cholesterol decreased 41 mg. %. The peak depression was noted in two weeks, with a mean reduction of 61 mg. %. The level then remained fairly constant through the fourth week, at which time the average cholesterol level depression was 57 mg. %.

The over-all results in 36 subjects showed a mean cholesterol depression of 35 mg. % after one week of therapy, which then progressed to a maximum of 58 mg. % by the fourth week.

Figure 3 summarizes the change in total cholesterol as related to time and dosage. A significant drop is noted in one week at all dosage levels. Although a further depression occurs by the fourth week, the rate of fall is sharply diminished. The heavy solid line indicates the mean drop for all dosage levels combined. The vertical lines represent 1 standard deviation of the mean for the respective time intervals.

There was some indication that the maximum decline was not reached until after the first week. However, the additional decline from the first to the fourth week was not statistically significant. In any event, there was no evidence of any tendency to return to the control levels at any time during the four-week period.

TABLE 2.—*Distribution of Patients as to the Absolute Reduction in Serum Cholesterol*

Change in Total Cholesterol, Mg. %	Subject, No.	Subjects, %
−200 to −151	1	3
−150 to −101	5	14
−100 to −51	16	44
−50 to −1	10	28
0 to +49	3	8
50 to +99	1	3
Total	36	100

Table 2 shows the distribution of changes from control levels to the four-week post-treatment period. These results are obtained from all dosage levels combined. It is noted

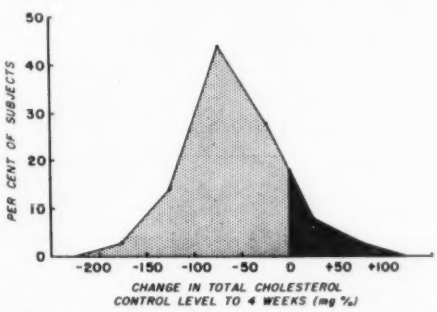

Fig. 4.—Graphic summary of the distribution of patients showing reduction in serum cholesterol; distribution of changes from control level to four weeks post treatment. (All dosage levels combined.)

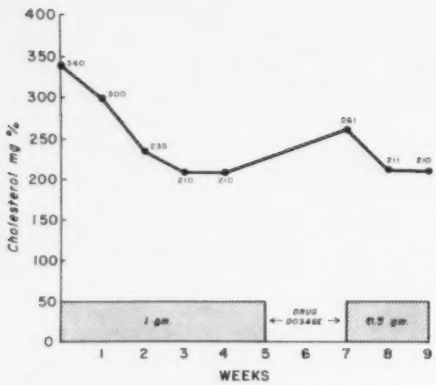

Fig. 5.—Effect of Mer-29 on the serum cholesterol in a patient in whom the drug was temporarily discontinued and then started again.

that a depression in serum cholesterol was present in 89% of the total subjects. In only 11% did the cholesterol level show no change or an elevation.

The distribution of changes in cholesterol level from controls is graphically pictured in Figure 4. The blackened area in the graph represents the distribution of those subjects who showed an elevation of serum cholesterol or no response to the drug. The dotted portion of the illustration represents the percentage of subjects who showed a depression in serum cholesterol.

In Figure 5, the response to the drug in an individual patient is demonstrated. An initial depressant effect on serum cholesterol was noted followed by a rise toward pretherapy levels when the drug was discontinued. Upon reinstitution of therapy, a significant lowering of the serum cholesterol was again seen.

The side-effects of the drug appear to be minimal in the dosages used. Nausea and vomiting were present in 13% (five) of the subjects at the higher dose levels, but it was unnecessary to discontinue the drug in any of the above subjects. An occasional patient with nausea and vomiting was relieved of his symptoms when the dose was reduced from 1,000 mg. to 500 mg. No gastrointestinal side-effects were noted when a dose of 250 mg. per day was used. No loss of weight occurred in any patient while on drug therapy. There was no evidence of hepatic or hemotoporetic toxicity.

Albuminuria was noted in 7% (three patients). The albuminuria was always minimal (not more than 2+) and was not seen in the low dosage range of 250 mg. per day, but this may have been coincidental. All of the patients showing albuminuria were elderly men, and low-grade prostatitis may have accounted for this finding. The albuminuria cleared with continuous administration of Mer-29, and there has been no other evidence of renal damage or drug toxicity. All other renal-function studies remained within normal limits. Recent work [13,14] also indicates that the albuminuria may be a false-positive reaction due to some metabolic breakdown product of the drug which is excreted in the urine.

One other subject developed a mild erythematous rash on his forearms, which disappeared spontaneously while he continued to receive the drug. No other side-effects were noted except for those previously described.

Summary and Conclusion

This is a preliminary report of Mer-29, a drug which inhibits cholesterol synthesis and which was administered to 36 patients. By virtue of its enzymatic inhibitory action on liver synthesis of cholesterol, the drug produced a statistically significant depression in the serum cholesterol concentration. The drug was well tolerated in the dosage levels used and was relatively free from toxic side-effects. It is concluded that Mer-29 is an effective drug for lowering serum cholesterol and warrants further investigation.

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Radioiodine in the Treatment of Hyperthyroidism

A Seven-Year Evaluation

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It is the purpose of this presentation to add a seven-year experience to the ever-growing literature of the treatment of hyperthyroidism with radioactive iodine. This experience with 294 consecutive patients has led to the formation of some opinions concerning several controversial aspects, such as minimum age for treatment, size of dose and dosage schedules, and effects of supplementary antithyroid drugs.

Material and Methods

A total of 294 patients (237 females and 57 males) with hyperthyroidism, from the Radioisotope Service of the Jewish Memorial Hospital, New York, and from our private files over the past seven years constitute the basis of this report. The diagnosis of hyperthyroidism was established by a complete history, physical examination, and an I^{131} thyroid profile.[1] The thyroid profile consists of a 24-hour uptake, conversion ratio, and measurement of the radioactivity of the saliva. In many instances a basal metabolic rate, chemical protein-bound iodine, and serum cholesterol determinations were included.

All patients were seen within six to eight weeks after the oral administration of I^{131}, or earlier if any untoward symptoms developed. The initial follow-up consisted of clinical and laboratory evaluation. The former included the patient's symptoms and a careful record of weight, pulse rate, blood pressure, grading of tremors, moisture of palms, state of the eyes, and the size and character of the thyroid gland. The size of the thyroid gland was estimated by palpation and recorded in grams, the accepted normal being 25 gm. Hertel exophthalmometer measurements were performed whenever exophthalmos was noted or suspected. Laboratory tests included the 24-hour I^{131} uptake and measurement of salivary radioactivity. The conversion ratio was omitted because of its recognized invalidity after I^{131} therapy.[1] Patients were followed every two months during the first year, and if remission persisted, the intervals were increased to six months and then to one year. In the entire series, 55 patients were observed for less than one year, 130 from one to two years, 33 for three years, 28 for four years, 24 for five years, 12 for six years, and 10 for seven years.

The dosages* in this study were expressed in rep† (roentgen equivalents physical), the commonly employed unit of absorbed radiation. A dosage schedule was established empirically, dependent upon three factors: the patient's age, the degree of clinical toxicity, and the character of the gland. Three arbitrary age groups were established, each of which was given an estimated dosage range as follows: up to 40 (young), 3,000-9,000 rep; 40-60 (middle), 6,000-12,000 rep; above 60 (old), 9,000-15,000 rep. The dosage within each age range was modified by the degree of clinical toxicity; the more toxic patient received a smaller dosage. Similarly, patients with diffuse, soft glands were treated with lower dosages than those with nodular glands. As an example, a moderately toxic patient with a diffuse soft gland in the middle age group was given a dosage of about 10,000 rep, whereas a similar patient in the young age group was given about 6,000 rep.

The dosage in rep was then translated into the dose in millicuries by means of the Marinelli-Quimby-Hines formula.[2] The formula is as follows:

$$\text{Dose } (\mu c.) = \frac{\text{rep} \times \text{wt. of gland (g)} \times \text{physical half-life}}{\% \text{ uptake} \times \text{effective half-life} \times \text{ergs}/\mu c/\text{gm. (tissue)}} = \frac{\text{rep} \times \text{wt. of gland} \times 8}{\% \text{ uptake} \times 5 \times 160} = \frac{\text{rep} \times \text{wt. of gland}}{\text{uptake}}$$

For example, the patient mentioned above, of middle age, with a diffuse, soft gland weighing 50 gm.

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* In this discussion, the "dose" is the administered millicuries and the "dosage" is the amount of absorbed radiation in rep.

† 100 rep=93 rad.

and an uptake of 60% should receive 10,000 rep. Solving the formula:

$$\mu c = \frac{10{,}000 \times 50}{60}$$

μc=8,300 or 8.3 mc.

In a more recent group of patients, subsequent to 1953, the effective half-life of I^{131} was calculated by measuring residual radioactivity in the gland four days after the administration of the therapeutic dose and extrapolating. In order to determine whether the effective half-life would be prolonged, a group of patients was routinely given strong iodine (Lugol's) solution 24 hours after the therapeutic dose and maintained on it for one week. When the severity of the disease warranted immediate control, antithyroid therapy (strong iodine solution or propylthiouracil) was given for a period up to eight weeks.

Results

TABLE 1.—The oldest patient was 78; the youngest, 16, and it is to be noted that 86, or 29%, of the total were below the age of 40. Earlier writers stressed this arbitrary dividing line on various grounds, but more recent reports tend to minimize this artificial boundary.[3]

TABLE 1.—*Age Distribution*

Age	Cases, No.
Below 20	2
21-30	34
31-40	50
41-50	79
51-60	75
61-70	40
71-80	14

The early fear that cancer might be produced by radiation from the I^{131} has not materialized. In any individual case, one must weigh the theoretical risk inherent in the use of ionizing radiation against the risk of any other modality of treatment. Although there have been reports of thyroid cancer following x-irradiation of the thyroid,[4-6] to date no authentic instance of thyroid cancer developing as a result of I^{131} therapy for hyperthyroidism has been published. The incidence of leukemia after I^{131} therapy, also a theoretical risk, has been shown to be no greater than in the general population.[7]

Another theoretical risk is that of producing gene mutation by irradiation of the gonads by blood-borne I^{131} before its localization in the thyroid. An x-ray of the lumbosacral spine will equal, and a gastrointestinal series will give three to four times, the 1.25 rad that a 10 mc. dose of I^{131} will deliver to the ovaries.[8] The above diagnostic radiologic procedures have been used for many years without evidence of causing gene mutation. That the whole question of gene mutation may be exaggerated is suggested by the studies of Kaplan,[9] who gave x-irradiation of the order of 70-80 rad directly to the ovaries in the treatment of anovulatory sterile women. In his series of 800 cases, 3 instances of minor malformation appeared. Since the statistical incidence of malformed births is considerably greater than this, we may conclude that the comparatively tiny dose of radiation received from blood-borne I^{131} following therapy of hyperthyroidism would exert no deleterious effect. Five of the patients in our series have conceived and have been delivered of normal offspring after receiving therapeutic doses of I^{131}.

TABLE 2.—Ninety-five patients (32%) presented thyroid glands that were not palpably enlarged. Moderate enlargement (30-50 gm.) was noted in 121 cases, and in 48 instances there was marked increase in size (above 50 gm.). Thirty post-thyroidectomy patients presented variable gland enlargements, ranging from barely palpable glands to diffuse goiters or recurrent nodular swellings.

TABLE 3.—Diffuse goiter was seen in 193 patients, while nodular toxic goiter was present in 71. The remaining 30 were post-thyroidectomy cases.

TABLE 2.—*Size of Gland*

Size	Cases, No.
Normal (0-25 gm.)	95
Moderate (30-50 gm.)	121
Large (50-100 gm.)	48
Post-thyroidectomy	30

TABLE 3.—*Character of Gland*

Character	Cases, No.
Diffuse	193
Nodular	71
Post-thyroidectomy	30

TABLE 4.—*Previous Treatment*

Type of Treatment	Cases, No.
Propylthiouracil	43
Strong iodine solution	17
Methimazole	12
Post-thyroidectomy	30
Combination	16
None	176

TABLE 4.—Of the total of 294 patients, 176 came under our observation for initial treatment with radioactive iodine, having received no previous antithyroid therapy. Thirty patients, or 10.2%, had had thyroidectomies previously, one as recently as 4 months and another 23 years prior to observation. Propylthiouracil in varying doses and for periods up to two years had been administered to 43 patients. Strong iodine solution had been given to 17 cases, methimazole (Tapazole) to 12, and combination therapy to an additional 16 patients.

TABLE 5.—*Response by Total Dose*

	Diffuse		Nodular		Post-Thyroidectomy	
Dose, Mc.	Improved	Failure	Improved	Failure	Improved	Failure
1.0-3	31	1	6	0	11	1
3.1-4	30	2	7	0	2	0
4.1-5	31	3	7	0	1	0
5.1-6	25	1	9	0	5	1
6.1-7	14	2	7	0	1	0
7.1-10	15	0	11	1	4	0
10.1-20	28	2	15	3	3	0
20.1-	2	0	1	2	1	0

TABLE 5.—This Table demonstrates the difference in the response between diffuse and nodular glands. The diffuse toxic thyroid was made to regress with relatively small doses. The Table indicates that 117 patients of 184, or 63%, with diffuse goiter needed 6 mc. or less, while only 29 patients, 42%, with nodular glands responded favorably to a similar dose. The dose levels were generally lower than those proposed by other authors.[10] The higher dose levels represent the summation of multiple therapies administered to patients who failed to respond to the initial small dose.

TABLE 6.—Analysis of this Table shows that approximately two-thirds of the total cases (194 of 294) were controlled by a single dose; two-thirds of the remaining cases (64 of 100) were controlled by a second dose; two-thirds of this remainder (25 of 36) needed a third dose; two-thirds of this remainder (8 of 11) needed one more dose. In other words, a person had

TABLE 6.—*Number of Doses*

	Diffuse		Nodular		Total	
Doses, No.	No.	%	No.	%	No.	%
1	149	70.0	45	58.0	194	66.0
2	41	19.0	23	29.0	64	22.0
3	17	8.0	8	10.0	25	7.5
4	6	2.0	2	2.0	8	3.0
5	1	0.5	1	1.0	2	1.0
6	1	0.5	0	0	1	0.5
Total	215	100	79	100	294	100

TABLE 7.—*Interval Between Treatment and Response*

Interval, Mo.	Cases, No.
2	53
2-3	113
3-4	42
4-6	29
6	24

a 66% chance of control with a single dose; of the one-third not controlled, there was a 66% chance that a second dose would achieve clinical remission. A patient stood a 2:1 chance of being controlled by any individual dose.

The diffuse goiters did somewhat better than the nodular; 70% of diffuse compared to 57% of nodular received only one dose. One diffuse and one nodular goiter needed five doses, and one diffuse case required six doses (totaling 36 mc.) before control was achieved.

It is interesting to note that 88% of all patients, diffuse and nodular, were controlled by one or two doses. Similar results were reported by other investigators.[11]

TABLE 7.—This Table corroborates the experience of others that improvement, if it occurs, is often evident quickly. In 63% of the cases, a positive response, judged by clinical signs and symptoms and by the I^{131} uptake and saliva count, was already evident by the end of the third month after the therapeutic dose. The patient who manifested slow improvement was watched for a period up to six months before a second therapeutic dose was given. However, if toxicity was still severe at the end of three months, additional therapy was considered.

TABLE 9.—*Exophthalmos*

Severity	Cases, No.	Results		
		Improved	No Change	Worse
+	21	8	13	0
++	28	14	14	0
+++	15	6	8	1
++++	17	10	6	1
Total	81	38 (48%)	41 (50%)	2 (2%)

TABLE 8.—*Remissions Maintained*

Time, Yr.	Cases, No.
1	75
1-2	68
2-3	41
3-4	32
4-5	30
5-6	14
6	1
No follow-up	13

TABLE 8.—The patients followed in this series maintained remissions for periods up to seven years. As indicated in this Table, the toxic thyroid patient controlled for one year rarely showed recrudescence.

TABLE 9.—In this study, there were 81 cases of exophthalmos of various grades of severity. The extent of severity was classified 1 to 4+, as determined by Hertel exophthalmometer measurements and clinical observation. There was improvement in 48%, no change in 50%, and moderate aggravation in 2%. To date, the initial appearance of exophthalmos after a maintained remission has not been observed.

TABLE 10.—The end-results are recorded in Table 10. Clinical remission was induced in 93%, of whom 85% were made euthyroid and 8% were made hypothyroid. These figures compare favorably with recent studies of Werner and Quimby,[11] Bierwaltes and Johnson,[10] McCullagh,[12] and Quimby, Feitelberg, and Silver.[3] In the successful therapy of hyperthyroidism with I^{131}, as with surgery, a certain percentage of hypothyroidism is inevitable. The 24 patients who became hypothyroid were, therefore, included as successes. The results in this series confirmed the observations of most others that the toxic nodular thyroid in general required larger doses for clinical remission (Tables 5 and 6).

TABLE 10.—*Results*

Character of Gland	Improved	Failure
Diffuse	170 (93%)	12 (7%)
Nodular	63 (91%)	6 (9%)
Post thyroidectomy	28 (93%)	2 (7%)
Lost to follow-up	13	—

TABLE 11.—*Effective Half-Life*

	Post Therapy				
	Iodine		No Iodine		
Days	No.	%	No.	%	Total
1	1	1	0	0	1
2	17	22	7	13	24
3	20	25	10	19	30
4	19	25	17	32	36
5	9	11	10	19	19
6	6	7	2	4	8
7	6	7	5	9	11
8	2	2	2	4	4
Total	80	100	53	100	133

TABLE 11.—The effective half-life, the time required for one-half of the radioactivity present in the thyroid to disappear from the gland, is a factor in the Marinelli-Quimby-Hines formula and was calculated in 133 patients. Since there is no correlation between the effective half-life as calculated from a tracer dose and that found in therapy doses, measurements can be made only after treatment.[13]

A group of 80 patients was given strong iodine solution, 5 drops t. i. d., for one week, beginning 24 hours after the treatment dose, to see if this would alter the effective half-life. Obviously, the longer the effective half-life, the longer the radioactive material will remain in the gland and, presumably, the better will be the result. Study of Table 11 shows that 61% of those patients receiving strong iodine solution and 70% of those not receiving it had an effective half-life of three to five days. The administration of stable iodine, therefore, did not influence the effective half-life and similarly, did not alter the ultimate clinical response.

Recently propylthiouracil is being used to control the severely toxic patient until the I^{131} becomes effective. This procedure is advantageous because it permits retracer studies within one week after withdrawal of the medication, in contrast to the three- to four-week period necessary when stable iodine is used.

TABLE 12.—*Complications*

Complications	Cases, No.
Thyroiditis	4
Crisis	1
Loss of hair (transient)	5
Hypothyroidism	
Early	18
Late	6

The change in the size of the enlarged thyroid gland parallels clinical response. The diffusely enlarged thyroid gland will often return to normal size. Although many of the nodular goiters will also completely regress, more commonly, partial regression will occur, leaving residual nodularity.

TABLE 12.—The complications encountered are listed in Table 12. For statistical purposes, the 24 cases of induced hypothyroidism are listed as complications, although they were previously discussed as clinical remissions. There were 18 patients who developed hypothyroidism within one year and 6 who developed it subsequently. To date, no patient has become hypothyroid after three years of remission. Several early mild cases spontaneously reverted to euthyroidism within a short time. None of those that have persisted longer than three months have reverted to the euthyroid state. No correlation was found between the induction of hypothyroidism and the dose range or age of the patient. The doses ranged from 2.7 to over 20 mc. and the dosages from 5,000-24,000 rep. Bierwaltes and Johnson [10] reported a 20% incidence of temporary and permanent hypothyroidism in exophthalmic goiter with the use of a single large dose. However, it should be pointed out that in the fractionation dosage schedule the last dose, though small, may produce hypothyroidism.

Four patients experienced transient thyroiditis manifested by pain and tenderness over the thyroid gland and slight fever within two weeks after administration of the radioiodine. There were five cases, all female, four of whom became hypothyroid, who complained of various degrees of hair loss. Explanation of this phenomenon is

lacking. One case of thyroid crisis with ensuing death occurred in a severely toxic girl of 16 years. A similar phenomenon was reported by Nelson et al.[14] and Feitelberg et al.[15]

Summary and Conclusions

Two hundred ninety-four cases of hyperthyroidism were treated with radioactive iodine and observed over a period of seven years.

Twenty-nine per cent of the patients in this series were below the age of 40. It was not felt that I^{131} should be withheld from patients below 40, because the feared complications of thyroid cancer, leukemia, and gene mutation have not been substantiated to date. In any individual case, one must weigh the theoretical risk inherent in the use of ionizing radiation against the risk of any other modality of treatment.

An empirical dosage schedule in rep was assigned to arbitrary age groups and ranged from 3,000-15,000 rep. Variation in dosage within each age group depended on the degree of thyrotoxicosis and character of gland. The dosage in rep was translated to millicurie dose by means of the Marinelli-Quimby-Hines formula. With the use of this method, therapeutic doses averaged less than in most comparable series. The lower incidence of hypothyroidism might be attributed to the smaller doses. At the same time, the remission rate equalled that produced by much larger doses reported in other series. If carcinogenesis is related to the quantity of administered radiation, smaller doses would inevitably reduce even this theoretical risk.

Ninety-six patients, or 32%, presented thyroid glands that were not palpably enlarged.

There were 193 diffuse glands, 71 nodular glands, and 30 post-thyroidectomy cases.

A group of 176 patients had had no previous treatment, and 72 had received antithyroid medical therapy for periods up to two years.

The diffuse toxic thyroid gland was made to regress with relatively small doses of I^{131}. Actually, 63% of the total number of patients with diffuse goiters were controlled with 6 mc. or less, whereas only 42% of the nodular glands responded favorably to a similar dose.

Approximately two-thirds of the total number of patients were controlled by a single dose of radioactive iodine. Generally, a patient stood a two-to-one chance of being controlled by any individual dose. Eighty-eight per cent of all the patients, both with diffuse and nodular thyroids, were controlled by one or two doses of I^{131}.

In the over-all picture, improvement, when it appeared, was evident quickly. In 63% of all the patients a positive response was evident by the end of the third month.

The toxic thyroid patient who was controlled for one year or more rarely showed a recrudescence. The patients in this series maintained remissions up to a period of seven years.

Of the 81 cases with exophthalmos, 48% improved and 50% were static. Two cases showed moderate aggravation.

An over-all cure rate of 93% was observed. This figure includes 8% of cases rendered hypothyroid.

A group of 80 patients who were given strong iodine (Lugol's) solution, beginning 24 hours after the therapeutic dose, showed that the administration of this stable iodine did not influence the effective half-life, and similarly it did not alter the eventual clinical result.

Twenty-four patients (8%) became hypothyroid—eighteen within the first year. If hypothyroidism persisted for more than three months, reversion to the euthyroid state was not observed.

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Acute Renal Failure as a Complication of Acute Pancreatitis

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It is the purpose of this paper to emphasize the not infrequent occurrence of acute renal failure complicating acute hemorrhagic pancreatitis. Basic texts [1-6] and recent review articles [7-12] on pancreatitis make no mention of acute renal failure as a potential complication. Actual survey of the literature reveals very few reports of this combination of severe diseases. Lucke [13] listed acute pancreatitis among the miscellaneous causes of "lower nephron nephrosis" but did not elaborate further. A review of 22 cases of "renal anoxia syndrome," by Gaberman et al.[14] included two which followed acute pancreatitis; Varay [15] reported a single case and referred to three others. Swan and Merrill listed acute pancreatitis as the cause of one of 85 cases of acute renal failure.[16] Lynch [17] described pathologic lesions of renal tubular necrosis (attributed by him to microscopic fat-droplet emboli) in six cases of pancreatitis, but antemortem acute renal failure was not mentioned in the clinical descriptions of these cases. Four other patients have been individually reported [18-21] in whom acute pancreatitis and acute renal failure developed coincidentally following surgery. One of these [18] also received incompatible blood, and in another intravascular hemolysis was a possible etiologic factor, since distilled water was used as the irrigating fluid during transurethral prostatic resection.[19]

The five patients to be reported were seen at this hospital within a four-year period (1955 through 1958). During this same period 32 cases of acute pancreatitis and 63 cases of acute renal failure were hospitalized.

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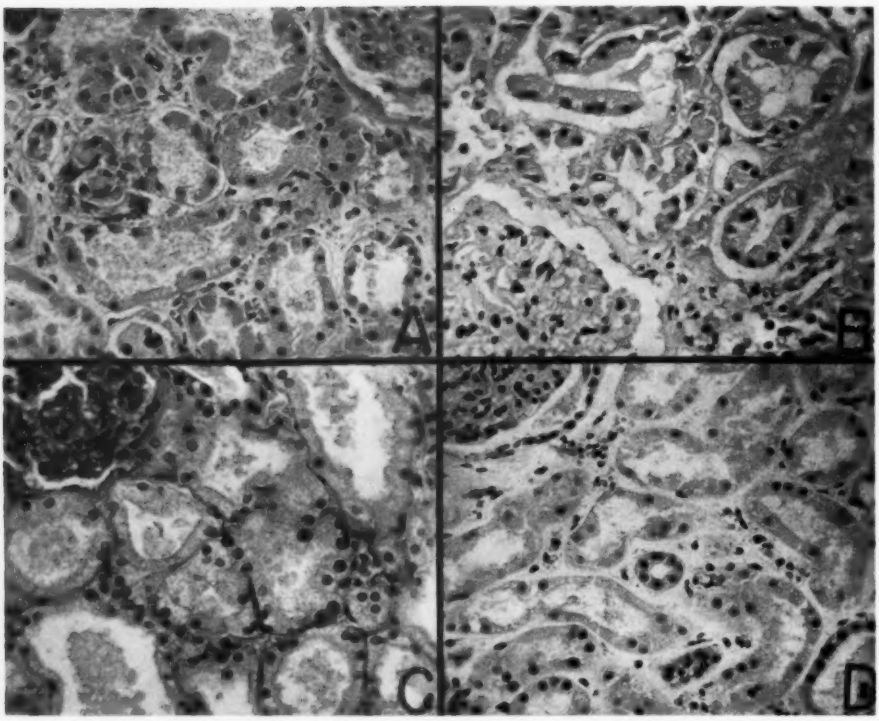
Report of Cases

CASE 1.—A 50-year-old white male Air Force Master Sergeant with a history of excessive alcohol intake over a period of many years first developed acute pancreatitis in 1954, confirmed by laparotomy and biopsy. Again, on Nov. 11, 1957, the patient developed severe abdominal pain, nausea, and vomiting after a prolonged alcoholic bout. He was admitted to another hospital, where his history, physical findings of an acute abdomen and shock, and a serum amylase of 1,100 Somogyi units led to a diagnosis of acute pancreatitis. Despite resuscitative efforts, shock persisted for 24 hours. Less than 200 ml. per day of urine was excreted, and after four days the patient was transferred to this hospital.

The patient appeared seriously ill, with a distended silent abdomen, a tender left upper quadrant mass, and bilateral patches of bluish discoloration in the flanks (Grey-Turner Sign). Admission blood urea nitrogen was 83 mg. %; serum amylase was 452 Somogyi units; serum potassium was not elevated. After daily total urine outputs of 60, 16, 130, and 365 ml., diuresis began on Nov. 19, with the excretion of 1,170 ml., at which time the blood urea nitrogen was 206 mg. %. His subsequent course, however, was complicated by the development of an infected pancreatic pseudocyst, Staphylococcus pyogenes var. aureus and Paracolobactrum septicemias, gastrointestinal hemorrhages, thrombocytopenia, purpura, and a terminal perilaryngeal hemorrhage on Dec. 19, 1957. Autopsy showed a subsiding acute pancreatitis, an infected pancreatic pseudocyst, and microscopic lesions of ischemic necrosis of renal tubular cells (Figure, *A*).

Comment.—Acute renal failure followed severe acute hemorrhagic pancreatitis and 24 hours of hypotension. Surprisingly, uremia and hyperkalemia progressed very slowly despite evidence of severe tissue



Representative views of the microscopic appearance of the kidneys, showing the pathologic changes of acute tubular necrosis. *A*, Case 1; *B*, Case 2; *C*, Case 3, and *D*, Case 4.

breakdown. In spite of a spontaneous diuresis on the eighth day of oliguria, a mild uremic state persisted until death.

CASE 2.—An 84-year-old white male retired Army Sergeant was admitted to this hospital on Sept. 26, 1956, because of severe abdominal pain, nausea, and retching of 48 hours' duration. He had not urinated since the day before admission. Episodes of abdominal pain had occurred sporadically for the preceding six months. There was no history of previous renal disease, alcoholism, or ingestion of any nephrotoxic agent.

The patient appeared acutely ill. The abdomen was distended and silent, and generalized tenderness and guarding without rebound tenderness or masses was present. There was no shock or icterus. A laparotomy was performed. The gallbladder was distended, and the pancreas was reddened, firm, and nodular. An amylase determination done on peritoneal fluid was 2,384 Somogyi units. The gallbladder was drained.

Postoperatively, the patient passed only 64 ml. of urine in 24 hours and thereafter failed to excrete more than 90 ml. per day. Because of increasing uremia and hyperkalemia, artificial hemodialysis was performed on Oct. 2, 1956. Oliguria persisted; uremia and hyperkalemia recurred, and melena and shock developed. Resuscitation with whole blood, oxygen, and norepinephrine (arterenol) was begun, and a second hemodialysis, performed. However, melena and shock recurred, and the patient died the following day.

At necropsy, peritonitis, biliary tract infection, retroperitoneal hemorrhage, acute necrosis of the pancreas, and an impacted stone in the common bile duct 10 mm. from the ampulla of Vater were found. Microscopic examination of renal tissue revealed arteriolar nephrosclerosis, with superimposed acute degenerative and regenerative lesions and pigmented casts compatible with ischemic tubular necrosis (Figure, *B*).

Comment.—This patient's pancreatitis was associated with a stone in the common bile duct which had not produced jaundice. Acute renal failure and pancreatitis preceded surgery. There was no documented episode of shock during the preoperative, operative, or immediate postoperative periods.

CASE 3.—A 44-year-old white medically retired soldier was hospitalized Dec. 25, 1954, because of an acute illness of five days' duration, manifest by intermittent abdominal pain, anorexia, weakness, and jaundice. He had passed "very little" urine for two days. During the preceding eight months, a daily pint or more of whiskey had served as the patient's major caloric source. A locally metastasizing carcinoma of the floor of the mouth had been previously treated with repeated courses of radiation.

On admission the patient appeared acutely ill, emaciated, and jaundiced. The mandible was partially replaced by an ulcerated mass with underlying adenopathy. Ascites and abdominal tenderness were noted. The liver and spleen were both enlarged and firm. There was edema of the abdominal wall, scrotum, and lower extremities. Admission blood pressure was 98/60; however, by the following day the blood pressure had fallen to 70/40.

The patient continued to run blood pressures in the range of 70-120/40-80 during the remainder of his course in the hospital. Urine excretion was less than 200 ml. per day until death, 15 days later. His terminal course was complicated by increasing uremia, hepatic coma, melena, pleuropericardial inflammation, bronchopneumonia, and a urinary tract infection.

Necropsy showed carcinoma of the floor of the mouth with metastases to local nodes, bronchopneumonia, pericarditis, ascites, portal cirrhosis with esophageal varices, and ulcerations of the gastrointestinal tract. In addition, numerous areas of hemorrhagic liquefaction were seen throughout the pancreas with varying degrees of fat necrosis. Examination of microscopic sections of the kidneys showed edema, bile staining, and acute tubular lesions compatible with ischemic necrosis (Figure, *C*).

Comment.—Acute pancreatitis was clinically unrecognized in this patient with predominant findings of severe liver and kidney disease. Acute renal failure developed prior to admission and persisted until death. The exact temporal relationship between the development of acute pancreatitis and renal failure could not be determined.

CASE 4.—A 40-year-old white male Master Sergeant awoke July 24, 1957, with nausea and vomiting. Abdominal pain developed and became progressively severer, centering in the epigastrium. Shortly after admission to another hospital the same night, the patient developed shock and a clouded sensorium. Admission hematocrit was 66%, and serum amylase was 1,066 units. Resuscitation was begun with intravenous fluids, albumin, and norepinephrine, but hypotension lasted several hours. During the first 24 hours the urine output was 200 ml.; it fell to 30 ml. the following day. The blood urea nitrogen rose to 150 mg. %.

On transfer to this hospital, on July 28, 1957, the patient appeared moribund. He was disoriented, febrile, and mildly cyanotic. Fine crepitant rales were present at both lung bases. The abdomen was distended and tender, and shifting dullness was noted. The liver was enlarged to 4 cm. below the costal margin, and the gallbladder was palpable. A bluish discoloration of both flanks was present (Grey-Turner Sign). Several hours after admission the patient became hypertensive; temperature rose to 105 F, and the patient died. Urinary output on the day of death was 250 ml.

At necropsy, the pancreas and its bed were almost entirely replaced by a firm hemorrhagic mass. Retroperitoneal tissues were edematous and necrotic. On microscopic examination of the kidneys, a diffuse interstitial edema and acute necrosis of tubular cells were present (Figure, *D*).

Comment.—Severe acute hemorrhagic pancreatitis was followed by persistent oliguria and a rapidly fatal course. Clinical acute renal insufficiency was confirmed by pathologic study of the kidneys.

CASE 5.—A 34-year-old Negro veteran was admitted to another hospital on Oct. 1, 1958, because of the acute onset of abdominal pain following a 24-hour alcoholic binge. He had an eight-year history of chronic alcoholism and at least a four-year history of hypertension. Acute pancreatitis was suspected immediately because of fever, absent bowel sounds, and epigastric tenderness. Serum amylase was elevated to 870 and rose to 1,200 units the following day. The patient was treated with nasogastric suction, intravenous fluids, and antispasmodics. Pulmonary edema occurred on the second day, following vigorous fluid administration. The patient was anuric on admission and remained so until his death.

During the first 40 hours of hospitalization, the patient had blood pressures at hypertensive levels. He then developed delirium tremens, and several hours later shock appeared. He was transferred to this hospital, where he appeared seriously ill. He was hallucinating, and diffuse muscular twitchings were noted. Admission temperature was 103.4 F; the pulse was 160, and the blood pressure was 50/0. There was abdominal tenderness, and bowel sounds were absent.

The patient continued to have blood pressures at shock levels in spite of continuous intravenous administration of pressor agents. He remained febrile with temperatures up to 106 F. Anuria continued, with the BUN mounting to 284 mg. % by the sixth hospital day, at which time he was dialyzed with the artificial kidney. Significant hyperkalemia

failed to develop. The serum amylase fell progressively to 192 units by the 14th day of illness. His subsequent course was characterized by progressive uremia and shock, with death on the 15th day of illness.

Necropsy showed bilateral cortical necrosis of the kidneys. The pancreas was markedly indurated with some hemorrhage, and there were areas of fat necrosis of the pancreas and omentum.

Comment.—Anuria in this patient was present at the time of his initial admission and preceded the documented period of shock. Unlike the oliguria of renal failure seen with acute tubular necrosis, complete anuria led to the antemortem suspicion of cortical necrosis, which was substantiated at necropsy. No similar case of cortical necrosis in association with acute pancreatitis has been reported to our knowledge.

Comment

Despite relatively few reported cases, acute renal failure complicating pancreatitis would not appear to be unexpected. The prolonged shock, hemoconcentration, and anoxia common in acute pancreatitis are all predisposing factors to the development of acute renal failure. While transient oliguria and prerenal azotemia can occur in acute pancreatitis, the danger of acute renal failure remains. This possible complication should be considered during resuscitative therapy of acute pancreatitis. Determination of hourly rates of urine production can be used as a guide to avoid overhydration of a patient who remains oliguric after shock is corrected. Although prerenal azotemia does occur after massive tissue necrosis, retroperitoneal hemorrhage, or dehydration, its severity does not approach that found in these five patients. Oliguria secondary to dehydration is corrected by rehydration; continued oliguria in these patients gave clinical evidence of acute renal failure.

When acute renal failure is superimposed on acute pancreatitis, the prognosis becomes very poor. Only the patient reported by Varay [15] was able to survive this dual insult. His age, 24, and the timely use of hemodialysis appeared to be major factors leading to survival.

An elevated serum amylase without associated pancreatitis has been noted in both acute [22] and chronic [23] renal insufficiency. Maximum serum amylase levels of 931, 1,388, 628, 325, 336, and 380 units/100 ml. (normal range, 60-160 units) in six cases of acute renal insufficiency were reported by Meroney et al.[22] These elevations were attributed to a diminished urinary excretion of amylase, although increased amylase production was also considered. Three of our patients had a repeat amylase determination several days after the onset of pancreatitis. While still abnormally high in Case 4, the serum amylase had fallen to normal in Case 2, despite continuing oliguria, and fell from 1,200 to 192 units in Case 5 during 12 days of anuria. In the case reported by Varay [15] the serum amylase fell from an initial 717 to 7 units on the 10th day of oliguria. Thus, it is evident that serum amylase can decline spontaneously despite continuing renal failure.

In spite of massive pancreatic necrosis, fever, dehydration, and, in two instances, acute hepatic necrosis, rapidly developing hyperkalemia was not a prominent feature of the acute uremia in four of our five cases, although the last patient was treated with potassium-removing resins after the third hospital day. We have no logical explanation for this observation, since in acute renal failure of other etiologies the serum potassium is known to rise rapidly when there are associated acute hepatic necrosis, febrile states, hypoxia, or massive muscle necrosis. It is of interest that the four cases referred to were all alcoholics. The failure to develop hyperkalemia rapidly is a fortunate circumstance in that hypocalcemia is common in both acute pancreatitis and acute renal insufficiency. Hence, cardiotoxicity to a rapid rise in serum potassium was not seen in these four cases.

Bilateral renal cortical necrosis is thought to have developed concomitantly with the onset of acute pancreatitis in one of our five cases. The anuria in this case occurred with the onset of abdominal pain and prior to the documented period of shock. Pan-

creatitis has not previously been reported as a cause of renal cortical necrosis.[24]

These five cases of acute renal insufficiency complicating acute hemorrhagic pancreatitis demonstrate the importance of early recognition of this complication in order that appropriate therapy may be instituted.

Summary and Conclusions

Five patients who developed acute renal failure in association with acute hemorrhagic pancreatitis are presented. Because of differences in medical management of the two conditions and the danger of treating acute renal failure as "dehydrated acute pancreatitis," it is suggested that the presence of progressive azotemia and persistent oliguria, despite the correction of hypotension and dehydration, be considered and treated as acute renal insufficiency until proved otherwise.

Finally, acute renal failure in association with acute pancreatitis is a very serious complication and makes the prognosis much less favorable.

Dr. F. K. Mostofi, Armed Forces Institute of Pathology, reviewed the renal pathology in all cases.

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Chronic Liver Disease with a "Lupus Erythematosus-like Syndrome"

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There have been reported in the recent literature a number of patients presenting with severe liver disease and a syndrome resembling systemic lupus erythematosus (S. L. E.).[1-7] Hypergammaglobulinemia, postnecrotic cirrhosis, or chronic hepatitis are common to all these patients. A few have had joint manifestations resembling rheumatoid arthritis. Jaundice often brings about remission in the activity of rheumatoid arthritis, and failure to do so in this group is of interest. The presence or absence of L. E. cells in these patients who have few to many of the clinical manifestations of S. L. E. has further confused the picture. Such a patient was recently studied at the University of Illinois Research and Educational Hospitals, and the details are reported in this paper. The symptoms, findings, and clinical course were those of S. L. E., but the usual pathological lesions of this condition were not found at postmortem examination. The principal findings were postnecrotic cirrhosis, pleuritis, and pericarditis. Microscopic examination of the lymph nodes showed peculiar "hematoxylin-like" bodies, which were laminated and were not considered to be the bodies found in S. L. E. Microscopic examination of the kidney did not show the changes reported in S. L. E. This patient had been treated with steroids for only nine days prior to death, and so it is not likely that therapy caused suppression of the pathological process.

In order to evaluate the above findings, we reviewed the autopsy and liver-biopsy material from 19 patients with proved S. L. E. In addition, the autopsy findings of 310 patients with cirrhosis and chronic hepatitis were examined. The criteria for the diagnosis of S. L. E. were fibrinoid degeneration of the collagen tissue, hematoxylin bodies, "wire looping" of the glomeruli, "onion skin" periarterial fibrosis of the spleen, and verrucous lesions of the endocardium. The usual criteria for cirrhosis and chronic hepatitis were used.

Systemic lupus erythematosus has been defined as a disease syndrome of unknown etiology involving the collagen tissue of any or all organ systems. Pericarditis, endocarditis, peritonitis, pleuritis, arthritis, hemolytic anemia, fever, nephritis, and encephalitis may be present individually or in various combinations. Liver involvement, however, appears to be minimal from a clinical as well as a pathological standpoint in most reported series.[8-11]

Harvey et al.[7] reported on 138 patients whom they considered to have lupus erythematosus. Of their patients, 48 had clinical hepatomegaly, 3 had unrelated portal cirrhosis, 2 had tuberculomas of the liver, and a few had some fatty degeneration, atrophy, and/or necrosis of liver cells of minimal degree. Only four of the patients were jaundiced, and in none was this shown to be due to the primary illness. In the entire series, only two patients had a lesion in the liver which could be related to

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S. L. E. In Griffith and Vural's [8] series of 18 patients, 6 had fatty degeneration, 1 had necrosis of the liver cells, and 6 had clinical hepatomegaly. Only one of Dubois' [9] patients had an arteritic lesion in the liver which could be attributed to S. L. E. Kofman, Johnson, and Zimmerman [11] reported on 25 patients with S. L. E., of whom 21 had a positive lupus-cell phenomenon. Six were examined post mortem. The findings of S. L. E. were present in five and the lesions of periarteritis nodosa in one. The livers of five other patients were examined by biopsy. Minimal nonspecific findings, such as small areas of necrosis, lymphocytic infiltration in the portal regions, mild inflammatory changes in the liver capsule, questionable prominence of Kupffer's cells, fatty metamorphosis, and congestion, were found. In one instance bile stasis associated with small granulomas was noted. This last patient was jaundiced.

Microscopic Findings in the Livers of Nineteen Patients with S. L. E.

Case	Finding
1	Fatty degeneration of liver
2	Normal liver
3	Chronic inflammation with lymphocytes, plasma cells, & some fibroblasts around portal areas
4	Fatty degeneration of liver
5	Fatty degeneration of liver, with lymphocytes, plasma cells, & some fibroblasts around portal areas
6	Healed tuberculomas of liver, with some central necrosis & passive congestion
7	Passive congestion, with lymphocytes and plasma cells in spaces & walls of blood vessels; mild fatty degeneration, & periductal infiltrates, with plasma cells & lymphocytes
8	Periportal round-cell infiltrate, with some fatty degeneration
9	Focal areas of necrosis, with moderate infiltrates of lymphocytes around portal areas
10	Hepatic cells in central areas of lobules shruken & replaced by swollen threads of acidophilic material which stuff sinusoids; fatty degeneration, with some degenerated fibrinoid material in periportal areas
11	Thickened capsule; distended central veins & sinusoids; fatty degeneration, & periportal mononuclear-cell infiltrate
12	Central veins & sinusoids increased in size, with increased amount of connective tissue around central veins
13	Bile-stained liver; cells of central zones replaced by fibrous tissue, with some collapse of architecture; bile stasis of central zones of liver, with small areas of focal fibrosis & mononuclear cell infiltrate
14	Central areas of lobules congested with some fatty degeneration
15	Congestion of liver
16	Fatty degeneration, with some lymphocytes around blood vessels
17	Passive congestion of liver sinusoids, with some arteriolar hyaline thrombi
18	Congestion of central veins, increase in fibrosis in periportal areas, & some fatty degeneration
19	Some increase in fibrosis around periportal areas

We reviewed the microscopic liver findings in 19 patients with proved S. L. E. who died at the Research and Educational Hospitals between 1940 and 1958. Some of these were included in the paper of Kofman et al. Our findings are shown in the Table. It should be noted that several different processes often occurred in a single liver.

In summary, fatty degeneration of mild to moderate degree was present in nine; periportal round-cell infiltrates of lymphocytes and plasma cells were found in seven; some degree of congestion of the central veins and sinusoids occurred in six. There was some increase in fibrosis of the periportal areas in three, fibrosis around the central vein in three, minimal necrosis focal in nature in four, healed tubercles in one, bile stasis of the central zones in another, and arteriolar hyaline thrombi with some fibrinoid material in the periportal areas in one. Six of these patients had hepatomegaly; one was jaundiced, and one had a normal liver.

With reference to the present problem, two types of reports can be gathered from the recent literature. The first group deals with patients having active chronic hepatitis with positive clot test for L. E. cells,[2-4] and the second group deals with young females having arthritis, periodic fever, disturbed menses, hypergammaglobulinemia, either chronic active hepatitis or postnecrotic cirrhosis, and, in some instances, serositis and positive tests for L. E. cells.[5,6]

The question raised by these reports is whether these patients have separate conditions or have atypical S. L. E. Some workers have minimized this latter possibility. Bartholomew et al.[6] have suggested that these patients may eventually be shown to have systemic lupus erythematosus.

Report of a Case

A 14-year-old Negro girl, admitted to the University of Illinois Research and Educational Hos-

pitals on Nov. 14, 1957, was in good health until 1952, when, following an upper respiratory infection, intermittent arthritis of the interphalangeal joints of the hands and wrists developed. In 1953, frequent epistaxis first appeared. In September, 1957, she was admitted to her local hospital with the complaints of sore throat, fever, malaise, and cough. She did not respond to management. Two months later, abdominal swelling associated with upper abdominal pain developed. Rectal temperature at that time was 104 F, and she was again hospitalized. At this time she had a transient loss of vision. It is of interest that in 1954 she had a pruritic skin eruption on both legs. Residual hyperpigmentation of the involved areas has persisted.

On admission to the Research and Educational Hospitals, physical examination showed a chronically ill Negro girl in no acute distress. The blood pressure was 118/30 mm. Hg; the pulse rate was 116, and the rectal temperature was 102.6 F.

The skin was hot and dry, and there was a hyperpigmented crusted lichenified rash on both lower extremities. There were bilateral enlarged nontender freely movable cervical nodes. The heart did not appear to be enlarged; the apex beat was felt 9.0 cm. to the left of the midsternal line. A loud harsh systolic murmur was heard over the entire precordium. Bilateral costovertebral angle tenderness was present. The liver could not be palpated. The spleen was felt 9 cm. below the left costal margin and extended to the umbilicus. There was questionable clubbing of the fingers. There was no evidence of arthritis; the joints appeared normal, and subcutaneous nodules were not found.

The hemoglobin on admission was 6.3 gm. per 100 cc.; the hematocrit was 23%; the white blood cell count was 3,500 cells per cubic milliliter, and the differential count was 82% polymorphonuclear leukocytes, 15% lymphocytes, 2% monocytes, and 1% eosinophils. Examination of the blood showed targeting of the red cells, with a decreased number of platelets. There was no occult blood in the stools. The specific gravity of the urine was 1.020; the pH, 6.0; there was a trace of protein, and the Harrison tablet test was positive for bile. Microscopic examination of the urine showed 20-30 WBC per high-power field, 5 RBC per high-power field, and a few granular casts. There were 4 Kahn units present in the patient's serum. The total serum-protein value was 10.4 gm. per 100 cc., with the albumin 1.1 gm. per 100 cc. and the globulin 9.2 gm. per 100 cc. The total serum bilirubin was 3.0 mg. per 100 cc. The thymol turbidity was 19.3 units, and the cephalin flocculation was 4+ at 48 hours. The prothrombin time was 36.5 seconds, with a control of 14.5 seconds. The N. P. N. was 27 mg. per 100 cc.; the ASO titer, 0 units, and the sensitized sheep-cell agglutination test for rheumatoid arthritis was negative. Two L. E.-cell clot tests were negative. Serum electrophoresis showed a marked increase in γ-globulin, with a single sharp peak. All other proteins were diminished. A bone marrow examination was reported as showing normoblastic erythropoiesis, with a slight shift to the left in the myeloid series. Plasma cells were markedly increased and predominately mature, with a few immature cells. There was a slight increase in the number of eosinophils and a moderate patchy increase of lymphocytes with scanty cytoplasm. The hematologist's impression was that this represented a nonspecific marrow very suspicious for lymphosarcoma. The ECG was reported as normal. On fluoroscopic examination generalized cardiac enlargement was found. Electrophoresis showed Type A hemoglobin. The anemia was thought to be due to either a hemolytic factor or hypersplenism.

The diagnosis on admission was collagen disease, most likely S. L. E. On Nov. 17, 1957, three days after admission to this hospital, she had the sudden onset of chest pain, which was pleuritic in nature, and a pleural effusion was found on examination. Cloudy fluid containing many leukocytes was obtained by thoracentesis. No pathogens were recovered on culture. Prednisone therapy, consisting of 100 mg. daily, was instituted on Nov. 20. Some clinical improvement was noted, but two days later the patient complained of abdominal pain, and on the next day she was found in coma. A lumbar puncture showed an opening pressure of 290 mm. of water. A colloidal gold curve of 5552220000 was reported. On Nov. 29, 1957, after five days of coma, a diarrhea developed, and two days later, following a generalized convulsion, she died.

At autopsy, 1,000 ml. of clear yellow fluid was found in the peritoneal cavity. The left pleural cavity contained 900 ml. of brownish-white fluid. The pericardium was slightly thickened, and its left pulmonary surface was covered by a fibrinous exudate. The heart weighed 250 gm., and the valve leaflets were normal. There was a thickened yellowish-white fibrinous exudate over the pleural surface of the left lung. The spleen was enlarged and weighed 550 gm. The liver was remarkably small and weighed only 420 gm. (Fig. 1). The capsule was rough, granular, and deformed by brownish-yellow nodular masses. On section, the liver was moderately soft in consistency and there were uniform, small nodular masses throughout the parenchyma. Microscopic section showed small nodules of varying size (Fig. 2). In the portal areas and surrounding the nodules there was a marked increase in the connective tissue, which was infiltrated with lympho-

Fig. 1.—Cut section of the liver, showing a multilobular cirrhosis.

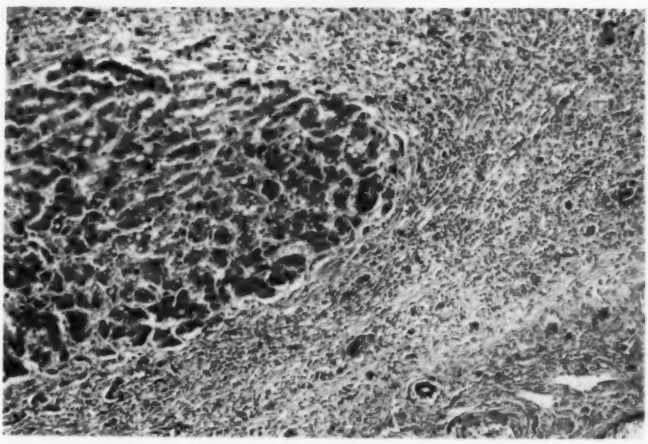

Fig. 2. — Photomicrograph of the liver, showing a regenerating lobule, broad bands of connective tissue, with proliferation of bile ducts and infiltration with lymphocytes and plasma cells. Hematoxylin and eosin; reduced 40% from mag. × 430.

cytes and plasma cells. Bile-duct-cell proliferation, some bile stasis, and extensive fatty metamorphosis were also present.

Sections of the lungs revealed widespread infiltration of the parenchyma with lymphocytes and plasma cells. The pleural surface showed a marked inflammatory reaction, with granulation tissue and plasma-cell infiltrates.

The lymph nodes showed reticuloendothelial hyperplasia, with infiltration of the sinusoids with

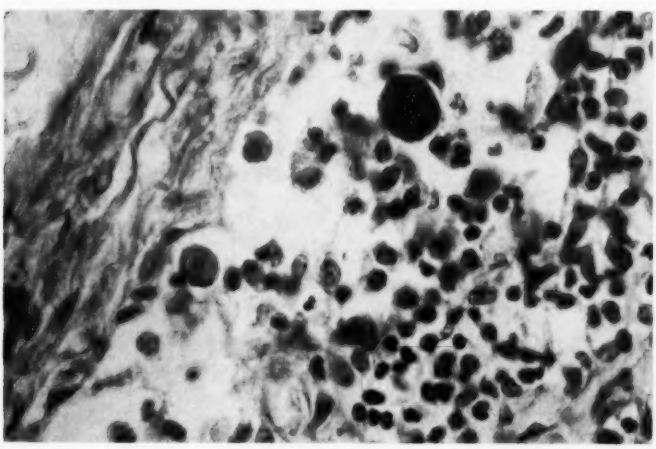

Fig. 3. — Photomicrograph of a lymph node, showing Russell-Fuchs laminated bodies which resemble the hematoxylin bodies of S. L. E. Hematoxylin and eosin, oil immersion; reduced 40% from mag. × 930.

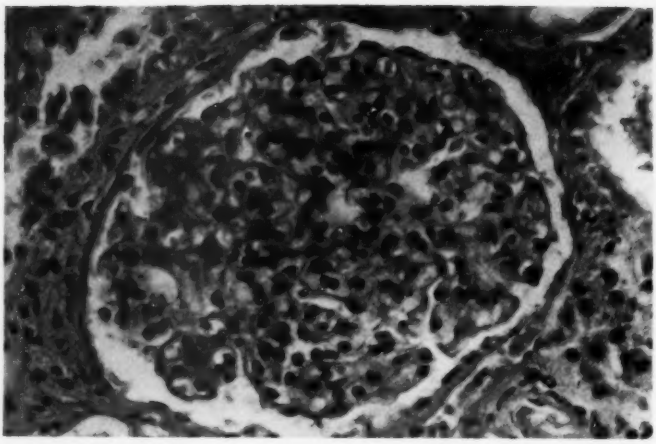

Fig. 4. — Photomicrograph of the kidney, showing absence of changes of S.L.E. Hematoylin and eosin; reduced 40% from mag. × 430.

Fig. 5. — Photomicrograph of the glomerulus of the kidney. There is no evidence of any basement membrane thickening. Periodic acid-Schiff; reduced 10% from mag. × 430.

histiocytes, lymphocytes, leukocytes, and plasma cells. There were also several small round purple "Russell Fuchs" bodies (Fig. 3). These resembled the hematoxylin bodies of lupus erythematosus, except that they were definitely laminated. The kidney glomeruli were slightly swollen and appeared anemic (Fig. 4). Bowman's spaces were narrow and contained granular eosinophilic fibrinous material. A periodic acid-Schiff (PAS) stain (Fig. 5) did not show thickening of the glomerular basement membrane. Examination of the spleen showed no periarterial fibrosis, and the findings were those of congestive splenomegaly.

The thick fibrosed pericardium was infiltrated with lymphocytes and occasional plasma cells. This process extended into the superficial interstitium of the myocardium.

The brain appeared normal.

The final anatomical diagnoses were as follows: (1) cirrhosis of the liver, with fatty metamorphosis; (2) pulmonary edema and emphysema, with atelectasis and bronchopneumonia; (3) subacute pleuritis, with organization; (4) subacute pericarditis, with interstitial myocarditis; (5) ascites; (6) hyperplasia of lymph nodes, with subacute inflammation; (7) congestive splenomegaly; (8) atrophy of adrenal cortices; (9) acute enteritis; (10) cholelithiasis; (11) acute hemorrhagic cystitis; (12) subacute esophagitis; (13) pigmented scars on the lower extremities.

Comment

Clinically this patient had many features of S. L. E., such as arthritis, pleuritis, splenomegaly, encephalopathy (loss of vision and convulsions), dermatitis, microscopic hematuria, false-positive serological test for syphilis, hypergammaglobulinemia, leukopenia, and anemia. Severe liver disease was not recognized during life. The terminal coma with convulsions was attributed to lupus encephalopathy. The very large spleen, bilirubinuria, and hypoprothrombinemia were more consistent with liver disease than with S. L. E. Of interest were the findings of infiltrates of plasma cells in the bone marrow and liver. The former have been seen in hypergammaglobulinemic states, and the latter have been reported by Kunkel et al.[12]

Review of the clinical and postmortem findings of 310 patients with cirrhosis or chronic hepatitis treated at this hospital did not show another patient with this syndrome.

The important morphological features that the liver of this patient showed were severe fibrosis, nodular regeneration, fatty metamorphosis, bile duct proliferation, and infiltrates of plasma cells, lymphocytes, and monocytes. In a review of our 19 patients with proved S. L. E., not one had a liver that showed this severe degree of disturbance of normal liver architecture.

The question that arises then is whether this is (1) lupus erythematosus with severe liver disease, (2) coincidental liver disease and systemic lupus erythematosus, or (3) a "lupoid-like" syndrome in severe chronic liver disease.

As a basis for the discussion of this syndrome, we believe the published case reports should be reviewed. Joske and King's[1] first patient had active chronic "viral" hepatitis, hypergammaglobulinemia, arthralgia, and a positive L. E.-cell phenomenon. A liver biopsy showed nodular regeneration of the liver lobules, with focal infiltrations of lymphocytes and plasma cells. A systematic search for L. E. cells was performed on seven patients with active chronic hepatitis and hypergammaglobulinemia. None of these patients had joint manifestations. One patient had a positive L. E.-cell phenomenon; three had erythrophagocytes with tart cells, and three patients had no L. E. cells. These authors believe that the positive L. E.-cell phenomenon in these patients is related to an immunological phenomenon as a by-product of the excess in γ-globulin production.

Heller et al.[2] had two patients with liver disease and positive lupus-cell phenomenon. Their Case 2 had pericardial effusion, anemia, elevation of the γ-globulin, pericarditis, and a positive Coombs' test. The liver showed subacute necrosis with cirrhosis. There was no histological evidence of S. L. E. Their other patient, who had alcoholic nutritional cirrhosis, was found during a routine survey to have L. E. cells.

Bettley[3] had a patient with elevated γ-globulin, L. E. cells, and a liver biopsy

specimen showing multilobular cirrhosis. This patient's bone marrow, similar to that of our patient, showed infiltration with plasma cells. There was no morphological evidence of S. L. E.

Mackay, Taft, and Cowling [4] considered their patients to have a condition which they chose to call lupoid hepatitis. They reported on seven patients, one of whom had previously been reported by Joske and King. Every one of these patients had a positive L. E.-cell phenomenon. The livers of all showed nodular regeneration of the lobules, with infiltrates of plasma cells and other round cells. Case 1 had chronic hepatitis, hypergammaglobulinemia, and a renal biopsy specimen that showed some thickening of the glomerular capillary walls; Case 2 had chronic hepatitis and a rash on the face; Case 3 had a cold-agglutinin-type hemolytic anemia, changes of rheumatoid arthritis of both knees, and a rash on the face; Case 4, who also had diabetes mellitus, on necropsy showed some nodular and diffuse thickening of the glomerular capillary walls; Case 5 was an adolescent boy with chronic hepatitis, and Case 6 had chronic hepatitis. Only one of these patients had joint manifestations.

Bearn, Kunkel, and Slater [5] reported 26 patients with a syndrome similar to that of our patient. Only one had L. E. cells in her serum, and none had morphological evidence of S. L. E. Arthritis was present in 11 at some time during the course of their illnesses and was the initial manifestation in 6. The morphology of the livers again revealed nodular regeneration, with infiltrates of plasma cells and lymphocytes.

Bartholomew et al.[6] had seven patients with either chronic active hepatitis or postnecrotic type cirrhosis. Every one had a positive lupus-cell phenomenon. The clinical picture in all was highly suggestive of a collagen illness. Five of the seven had arthritis; two had arthralgia; four had pleuritis; six had periodic fever; four had sensitivity to sunlight, and three had an erythematous rash on the face. The kidney in Case 1 showed moderate endothelial proliferation of the glomerular tufts, with increased segmentation of the tufts. The postmortem examination of Case 2 was done at another hospital. The authors were informed that this patient had lesions similar to those of S. L. E. Case 5 had a needle biopsy of the kidney, showing endothelial proliferation of the glomerular tufts with mild thickening of the basement membrane. Though the clinical picture was highly suggestive of S. L. E., the findings on postmortem and biopsy examinations did not warrant an unequivocal diagnosis of this condition.

Kunkel et al.[12] reported in 1951 on the serum-protein levels of 1,200 patients. Only 12 had elevated γ-globulin values, and 11 of these were females, the oldest being 32 years of age. These patients had high fever and arthralgia or arthritis. In nine, the livers showed a marked degree of plasma-cell infiltration. These authors felt that the globulin was identical to normal γ-globulin.

We believe that there has been a sufficient number of patients with this syndrome of severe liver disease and a "lupus-like" picture to eliminate the possibility of coincidental association of two diseases. The question arises then as to whether this is systemic lupus erythematosus or a separate entity. The finding of false-positive lupus-cell preparations in penicillin sensitivity,[13,14] serum sickness,[15] hydralazine therapy,[16-18] and chronic rheumatoid arthritis [19] is evidence against this being a specific serological test.

Some insight into the pathogenesis of this type of liver disease, with its manifestations imitating S. L. E., may be obtained from the work of Larson et al.[20] These workers characterized normal γ-globulin and the L. E.-cell-promoting factor by electrophoretic convection. The globulins were then put on an exchange resin. The elution patterns of the normal globulin and the L. E. factor were similar. By gel-diffusion techniques a single component similar to normal γ-globulin was found for the L. E.

factor. On boundary electrophoresis the L. E. factor had the same migration as normal γ-globulin. The ultracentrifuge sedimentation number of the L. E. factor was 7S, that of normal γ-globulin. It may well be that in hypergammaglobulinemic states with the overproduction of 7S globulins there is a rise in the factor which is responsible for the lupus-cell phenomenon.

Other hypotheses have been suggested. Burnett and Fenner [21] proposed that the virus of hepatitis so alters the liver cells that they are not recognized by the antibody-producing mechanism of the body, which then develops autoantibodies to the liver cells. This is in accord with the theory of Dameshek.[22] He suggested that an abnormal protein synthesis develops in what we call lupus erythematosus, producing autoantibodies to the collagen tissue which lead to the morphological changes responsible for the disease.

The question arises as to whether we are justified in considering a patient with severe liver disease and a clinical picture resembling lupus as having S. L. E. in spite of a paucity of morphological evidence on postmortem or biopsy examination. After long-term adequate suppressive steroid therapy one might expect little or no morphologic evidence of S. L. E. However, the reported cases have not had this type of therapy, and our patient was on steroid treatment for only 10 days. It is true that as we are better able to handle these patients with steroids, antibiotics, etc., they are living longer and sometimes dying from unrelated diseases. Our concepts of the pathology of S. L. E. possibly should be changed. However, it seems that with our present criteria, the diagnosis of S. L. E. in a patient presenting an atypical or incomplete syndrome in the absence of pathological changes on postmortem examination should not be accepted.

It is our feeling that one should keep an "open mind" on this subject and consider these patients as having an atypical form of liver disease with "lupoid" manifestations. In this way such patients will be studied more thoroughly and will not be considered as having atypical forms of systemic lupus erythematosus. Until the virus of hepatitis is isolated and characterized and the etiology of S. L. E. is established, the problem of whether these people with severe liver disease do or do not have S. L. E. will not be definitely answered.

Summary

A 14-year-old girl with arthritis, hypergammaglobulinemia, and other manifestations, constituting a "systemic lupus erythematosus (S. L. E.)-like" syndrome, was found on postmortem examination to have a severe postnecrotic cirrhosis with none of the usual histological findings of S. L. E. Review of the hepatic findings of 19 patients with proved S. L. E. showed only mild and nonspecific changes. None of them had evidence of severe liver disease. A survey of the postmortem findings of 310 patients with cirrhosis and/or chronic hepatitis did not show a single patient with a similar "S. L. E.-like" syndrome.

A number of patients with severe liver damage and an "S. L. E.-like" syndrome have been reported in the recent literature. These have in common chronic active liver disease and hypergammaglobulinemia. Many of them have had arthritis, positive lupus-cell phenomenon, and serous membrane involvement.

It is our opinion that these patients do not have S. L. E. but have a syndrome resembling this entity, due to an altered immunological reaction on the basis of severe active liver disease.

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Influence of Tropical Weather on Cardiac Output, Work, and Power of Right and Left Ventricles of Man Resting in Hospital

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It has been noted previously[1-4] that a warm and humid environment increases the output of the heart. Cardiac output was measured by the direct Fick method in five volunteer subjects resting in bed in wards of the Charity Hospital during the New Orleans tropical weather of July and August, 1957.[3] The cardiac output in all patients was found to be higher (mean about 50%) when they were in a warm and humid ward open to the outside weather than when in an air-conditioned and comfortable one. Because of the importance of these findings it was considered advisable to repeat these studies in five more volunteer patients during the New Orleans tropical weather of August, 1958. This report is concerned with the data obtained during the summers of 1957 and 1958.

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Materials and Methods

Five additional adult Negro subjects (Subjects 6 through 10), four of whom had no evidence of a cardiac disease and another (Subject 6) with hypertensive cardiovascular disease without heart failure, were studied about four hours after breakfast (Table 1). The conditions of the experiment were essentially similar to those previously described,[3] except that the mean temperature of the warm and humid ward was 90 F and the mean relative humidity 74% and the temperature of the comfortable, cool air-conditioned ward was 73 F

TABLE 1.—*Clinical Data on the Ten Hospitalized Adult Negro Patients*

Subject No.	Age, Yr.	Sex	Diagnosis	Treatment	New Orleans Weather at Post Office Station, U. S. Weather Bureau				
					Temp., F			R. H., %	
					Max.	Min.	Mean	Max.	Min.
1	41	M	Lesion, rt. middle lobe; etiology undetermined	Streptomycin, penicillin	88	77	83	87	47
2	63	F	Diabetes mellitus	Tolbutamide (Orinase)	91	74	83	96	63
3	42	F	Diffuse colloid nontoxic goiter	Strong iodine (Lugol's) solution, thyroid extract	94	79	87	92	46
4	48	M	Osteoarthritis, cervical spine	Acetylsalicylic acid	90	76	83	70	41
5	54	F	Rheumatoid arthritis	Symptomatic	95	78	87	91	43
6	39	F	Myxedema, CHF (compensated), LVH, myocardial ischemia	Digitalis, thyroid extract	94	79	87	90	48
7	58	F	Diabetes mellitus; chronic cholecystitis; def. ECG evid. myocard. dis.	Insulin, antibiotics	92	77	85	92	55
8	42	F	Chronic alcoholism	Vitamins, antibiotics	93	75	84	88	53
9	65	F	Gastroenteritis; hypothyroidism	None	93	71	82	86	36
10	32	F	Benign gastric ulcer	Antispasmotics, antacids	86	69	78	74	38
Mean					92	76	84	87	47

TABLE 2.—*Data Obtained on Ten Hospitalized*

	Cool Environment								
Subject No.	Room Temp., F	R. H., %	Blood Press., Mm. Hg Syst.	Blood Press., Mm. Hg Diast.	Pulse/Min.	O_2 Consumption, Cc/Min.	A-V O_2 Diff., Cc/100 Cc.	C. O., L/Min.	Stroke Vol., Cc.
1	74	47	135	85	58	179	3.8	4.7	80
2	76	67	128	82	92	139	3.8	3.6	40
3	72	49	165	100	106	259	4.0	6.4	56
4			96	70	68	52	3.3	1.6	26
5	72	60	135	75	88	151	2.3	6.5	73
6	75	55	190	110	78	119	5.5	2.0	48
7	75	70	185	120	83	257	4.6	5.6	67
8	75	66	175	115	118	110	4.9	2.2	19
9	70	55	190	100	68	127	4.2	3.0	44
10	72	65	185	110	68	167	4.1	4.1	60
Mean	73	59	158	97	83	156	4.1	4.0	51

and the relative humidity 62% (Subjects 6-10, Table 2). The variations in the temperature and relative humidity for each experiment are shown in Table 2. Variations in daily temperature and relative humidity, recorded on top of the Post Office Building, located about one-half mile from the Charity Hospital and reported by the U. S. Weather Bureau, are shown in Table 1. Since the experiments were conducted between 11:30 a. m. and 2:30 p. m., the maximum values prevailed at the time of these studies and were essentially the same as those recorded in the non-air-conditioned ward (Table 2).

The subject rested comfortably on a hospital roller while the cardiac output was measured by the Fick method, with use of right heart catheterization. Pressure recordings were utilized to guide catheter placement. The necessary measurements were made after the subject had been exposed for an hour or more to each environment. Half of the studies during 1957 and 1958 were conducted in the non-air-conditioned ward first and then in the air-conditioned ward, while the other half were conducted in the air-conditioned ward first and then in the warm one.

To construct the time-course curves of pressure for the left ventricle and of volume, pressure-volume, accumulative work, and power for both ventricles, it was necessary to make certain gross assumptions previously described.[5-8] The right ventricular pressure trace was the only curve recorded directly with suitable pressure transducers and recorder. The constructed traces must be cautiously evaluated in light of the gross assumptions.

Results

The results are summarized in Tables 2 and 3 and Figures 1-6.

The results obtained in the 10 subjects during the tropical weather of 1957 and 1958 in New Orleans were remarkably similar. The individual variations in cardiac output were fairly marked and in a range generally accepted for the experimental conditions. The cardiac output in the warm and humid ward was invariably greater than in the cool and comfortable air-conditioned ward. The mean cardiac output of the 10 subjects was 4.0 liters per minute in the air-conditioned ward and 5.7 liters per minute or 57% greater, in the warm and humid ward, where they were exposed to tropical weather (Table 3 and Fig. 1). All patients felt much better generally when in the air-conditioned ward.

The mean systolic and diastolic blood pressures for the 10 subjects were lower when in the warm and humid ward, while the pulse rate for the group did not change

TABLE 3.—*Influence of Tropical Weather on Cardiac Output in Ten Hospitalized Adult Negro Patients at Rest in Hospital*

	Cardiac Output, L/Min.		
Subject No.	Cool Ward	Warm Ward	Increase, %
1	4.7	6.4	36
2	3.6	5.0	39
3	6.4	7.8	22
4	1.6	3.9	144
5	6.5	8.6	32
6	2.0	4.1	105
7	5.6	6.8	21
8	2.2	3.2	45
9	3.0	5.6	87
10	4.1	5.7	39
Mean	4.0	5.7	57 (Ave. of 10) 43 (increase in mean)

Adult Negro Patients at Rest in Hospital

Warm & Humid Environment

Room Temp., F	R. H., %	Blood Press., Mm. Hg Syst.	Diast.	Pulse/Min.	O_2 Consumption, Cc/Min.	A-V O_2 Diff., Cc/100 Cc.	C. O., L/Min.	Stroke Vol., Cc.
92	76	135	80	60	365	5.7	6.4	103
91	65	120	84	104	149	3.0	5.0	53
91	58	125	77	101	250	3.2	7.8	65
		108	62	64	153	4.0	3.9	62
99	70	126	74	88	222	2.6	8.6	97
91	62	200	120	85	200	4.9	4.1	52
92	74	135	60	75	258	3.8	6.8	90
91	68	175	110	124	133	4.2	3.2	26
90	71			75	236	4.2	5.6	75
87	93	160	95	77	208	3.6	5.7	74
92	71	143	85	85	217	3.9	5.7	70

significantly. Thus, the cardiac output was greater in the warm and humid environment because of a greater stroke volume. Because the blood pressure tended to be lower in the warm and humid environment, cardiac work did not increase proportionately with the increase in cardiac output, and in an occasional subject it even decreased.

The calculated pressure-volume-time diagram and the work and power curves (Figs. 2-6) indicate the influence of the warm and humid environment upon the manifested work of the heart in three selected subjects. It can be seen from Figure 5 that the work of the right and left ventricles of Subject 6 was less when she was in the cool air-conditioned ward than when she was in the warm and humid ward. Subject 7, on the other hand, showed little difference in manifested cardiac work for both environments even though cardiac output was greater in the warm and humid environment than in the comfortable one (Fig. 6). The right ventricle of Subject 10 performed greater work when she was in the warm and humid environment than when in the cool one, whereas the left ventricle performed essentially the same amount of work in both environments (Fig. 4). The manifested work and power of the ventricles depended upon the simultaneous variations in time course of volume output and of pressure during the cardiac cycle (Figs. 2 and 3).

Comment

The studies during the midsummers of 1957 and 1958 showed that a warm and

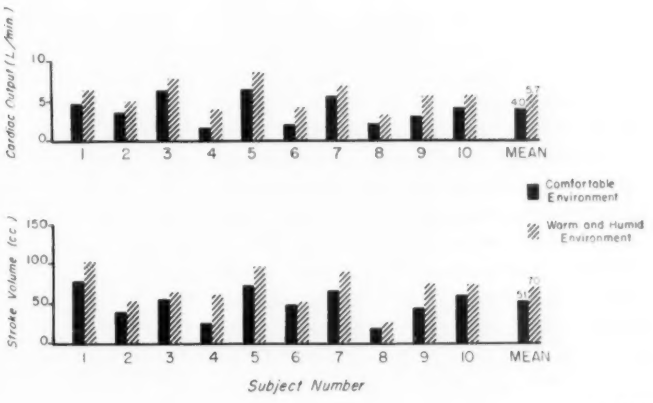

Fig. 1.—Influence of tropical weather on cardiac output and stroke volume in 10 Negro patients at rest in hospital.

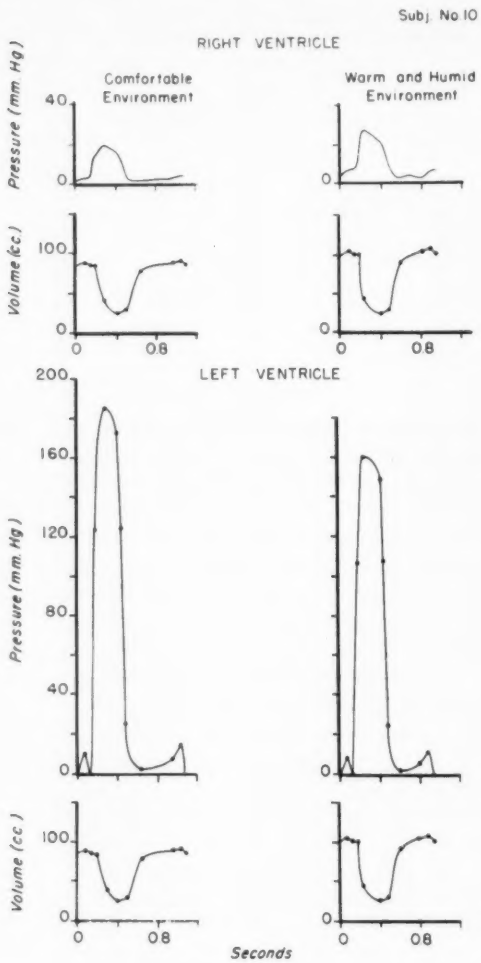

Fig. 2.—Influence of tropical weather on calculated curves, time-course of pressure, and volume in Subject 10. Only the pressure curves for the right ventricle was recorded directly.

humid tropical environment produced a greater cardiac output than a cool and comfortable, air-conditioned one. This observation was invariably true for the 10 subjects studied. All subjects felt considerably better in the cool and comfortable air-conditioned ward. These data indicate that air-conditioning of the environment of the patient with heart disease and the debilitated patient is of benefit to him even when at rest in bed. Psychic and physical exertion with the additional work demanded would only exaggerate the benefits of a cool and comfortable environment over a warm and humid one.

It is interesting to note that all of the subjects had been in New Orleans throughout at least the previous year, and, although partially acclimatized to the summer weather, they did not maintain the same cardiac output in both environments. Furthermore, all subjects were Negroes, who are generally considered to be able to cope readily with a warm and humid climate. It was not possible to determine from these studies whether or not the greater cardiac output in the warm and humid environment is a manifestation of a physiologic need to meet the demands of the warm and humid en-

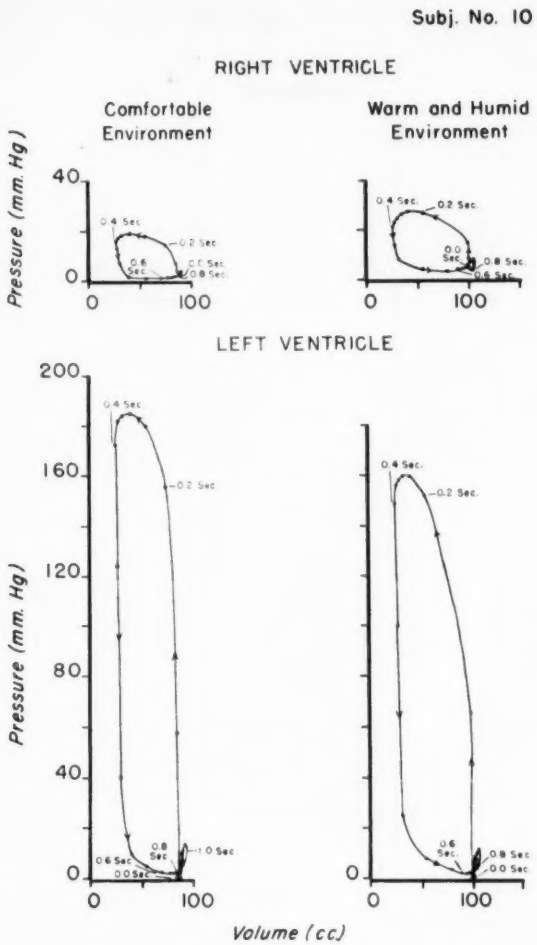

Fig. 3.—Influence of tropical weather on pressure-volume-time course curves in Subject 10, calculated from the volume and pressure curve shown in Figure 2. These diagrams show the left intraventricular pressure to be lower, while that in the right ventricle is greater when the subject was in the warm and humid environment.

vironment or a lack of adequate acclimatization. It would appear that it is not only due to the latter.

It should be emphasized that the atmosphere during these studies was humid. The increase in cardiac work probably would not have been as great if the environment were warm and dry. This seems to be true from indirect estimation of cardiac work in this laboratory over the past 16 years and from the studies of others.[6]

The calculated time-course curves of pressure-volume, work, and power indicate the importance of knowing the time course of blood pressure as well as the time course of cardiac output during each cycle of the heart chamber under study. An increase in cardiac output does not necessarily indicate an increase in heart work. These curves also demonstrate the need for accurate recordings of the time course of both pressure and volume in order to know manifest work and power output of a cardiac chamber. Unfortunately, the time course of volume of the chambers of the heart of intact man, or any animal for that matter, cannot be readily and accurately recorded yet.

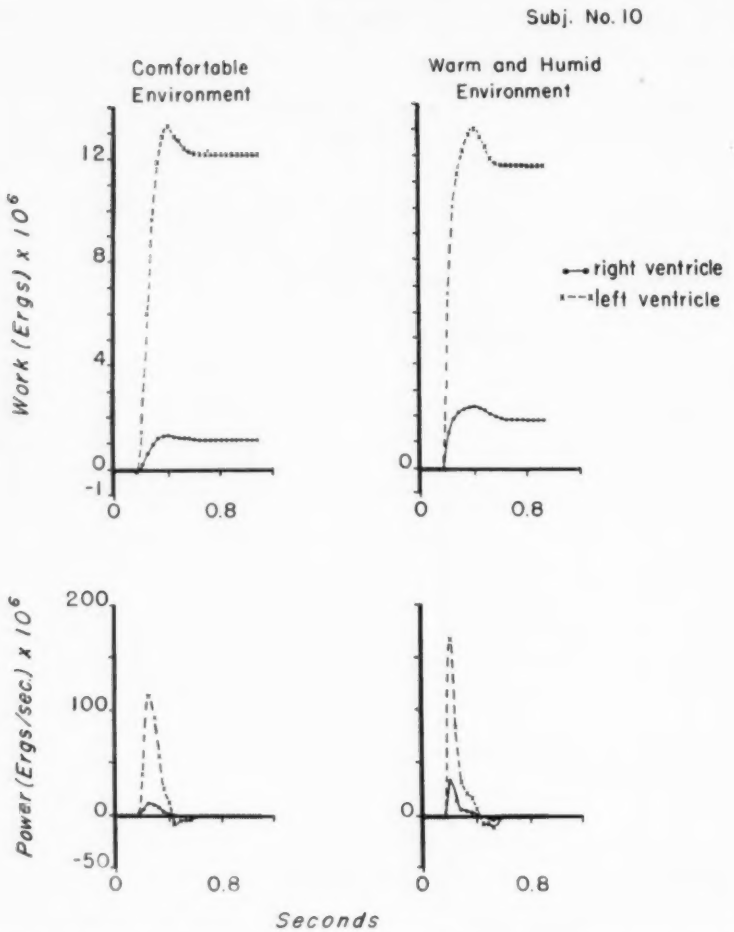

Fig. 4.—Influence of tropical weather on the time course of accumulated work and power in Subject 10, calculated from the diagram shown in Figure 3. Even though cardiac output was greater in the warm and humid environment, because of the associated decline in intraventricular pressure, the manifested work of the left ventricle, was not greater in the warm and humid environment than in the comfortable one; whereas, because of the associated increase in intraventricular right ventricular pressure, the simultaneously manifested work of the right ventricle was greater in the warm and humid environment than in the comfortable one. However, although the left ventricle performed essentially the same amount of work in both environments, the rate with which it performed work during systole was more rapid in the warm and humid environment, and so the peak power attained was greater in the warm and humid environment than in the comfortable one.

Summary

The cardiac output of five additional volunteer patients at rest on a hospital roller in the warm and humid tropical summer weather of New Orleans in 1958 was found to be about 57% greater than it was when the patients were at rest in a cool and comfortable air-conditioned ward. These findings were essentially the same as those noted during the summer of 1957 for five other patients. The data for both groups of patients are discussed.

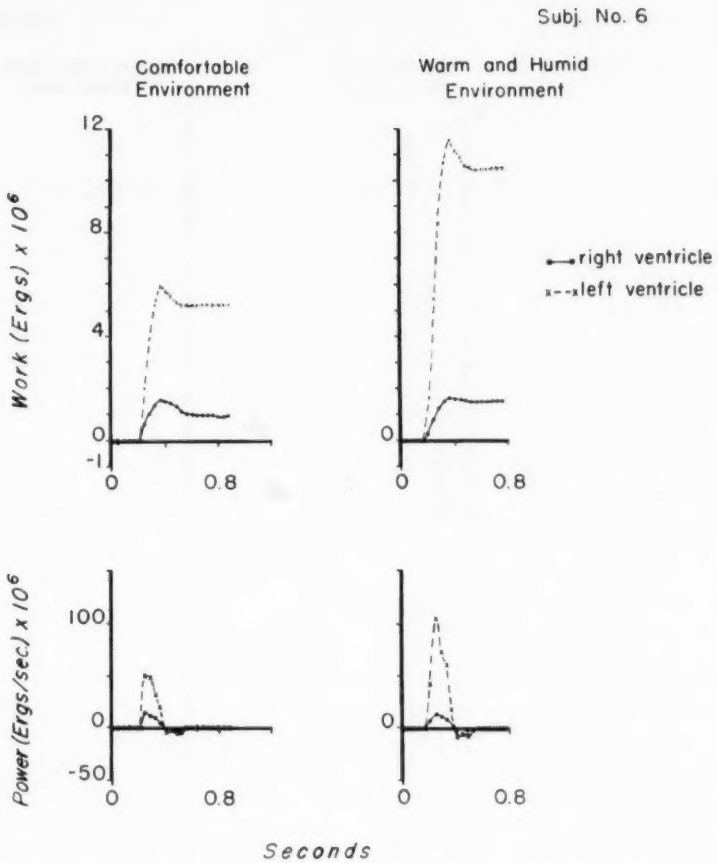

Fig. 5.—Influence of tropical weather on calculated time-course curves of accumulated work and power in Subject 6. Because of volume and pressure time relationships, the manifested accumulated work of the left ventricle was greater in the warm and humid environment than in the comfortable one, while that for the right ventricle remained essentially unchanged in spite of a greater cardiac output in the warm and humid environment.

Calculated time-course curves of pressure-volume, work, and power of the right and left ventricles indicate the need for accurate recordings of these parameters in intact man in order to know manifest cardiac work, cardiac work efficiency, and cardiac reserve. After necessary assumptions were made, calculated curves showed that an increase in cardiac output does not necessarily mean an increase in work if blood pressure is also changing. Furthermore, if pulmonary and systemic arterial pressures change discordantly, the work of one ventricle may increase, while that of the other may not increase as much at all or may actually decrease.

These studies of 1957 and 1958 show further the need for providing a cool and comfortable environment for the patient with heart disease, for whom cardiac rest is indicated in therapy. Air-conditioning of the hospital, home, and work area of the patient with heart disease needs emphasis.

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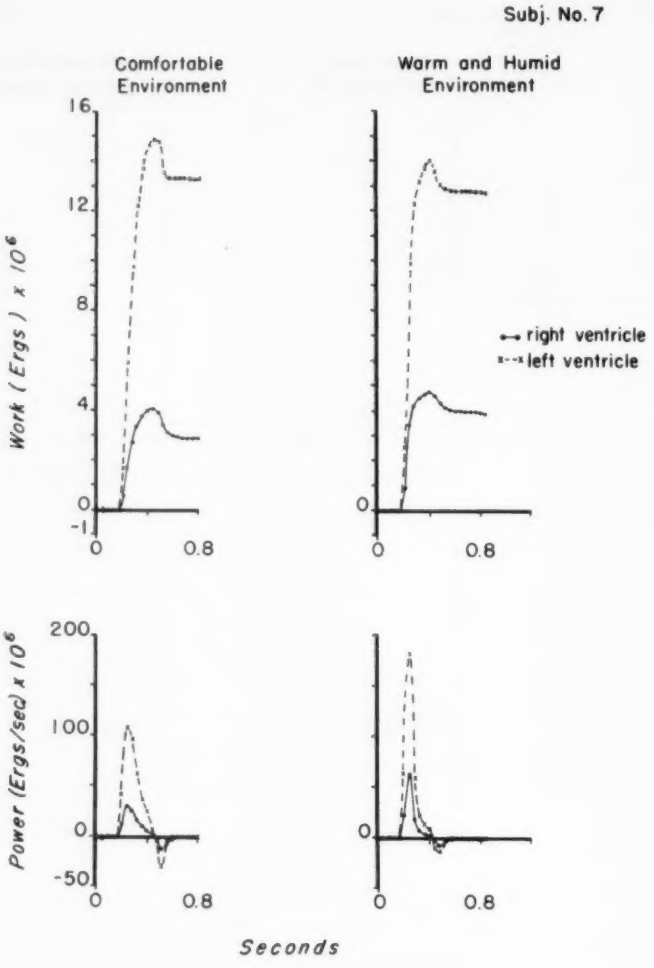

Fig. 6. — Influence of tropical weather on calculated accumulated work and power in Subject 7.

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Hydatid Disease

A Summary of Human Cases in Mississippi

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There is mounting evidence that the dog tapeworm, Echinococcus granulosus, is a major cause of human morbidity and mortality in many parts of the world. Shawkat [1] has stated, "In Iraq it is the Number One surgical problem," and, in 1957, Jidejian [2] wrote, "In Lebanon, the possibility of a hydatid cyst is considered in the differential diagnosis of any tumefaction." Bush,[3] in a 10-year study, reported 3,780 hospital admissions for hydatid disease in Uruguay, at a rate of about 400 per year. He also reported incidence rates of 100% in old ewes, 92% in sheep, and 80% in pigs.

The disease has long been a scourge in Australia and New Zealand (Graham [4]). Faust and Russell [5] called attention to its high endemicity in most of the pastoral countries of the world, including south Australia, Tasmania, New Zealand, Africa, and parts of South America. They also reported frequent infection in humans throughout Europe, Siberia, Turkistan, Mongolia, North China, Japan, The Philippines, Syria, Lebanon, Palestine, and Arabia. In February, 1958, the Pan-American Sanitary Bureau,[6] Regional Office of the World Health Organization, reported 4,049 cases in Argentina in the 10-year period ending in 1955. High incidence rates were also reported in Chile and Uruguay. Thus the parasite is practically worldwide in its geographic distribution.

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Each year there are repeated reports of the occurrence of hydatid disease in virtually every organ and tissue of the human body. The 1957 literature was typical of recent years and contained reports of its occurrence in such unlikely sites as the diaphragm (Velasco et al.[7]), the mediastinum (Rellan and Brea [8]), the pancreas (Boulvin [9]), the spinal cord (Chitkara [10]), the thyroid gland (Shopov [11]), the myocardium (Canabal et al.[12]), the carotid artery (Gessini and Giammusso [13]), and the kidney (Teplick et al.[14]). In the same year Jidejian [2] summarized the cases which had come to his attention in Lebanon. In his patients there was involvement of the liver in 178 cases, the lungs in 194, the kidney in 18, the spleen in 15, the brain in 4, the thyroid in 3, and the heart in 1.

E. granulosus was first observed on the North American continent by Low, in 1808, and again in 1811 (Magath, 1941 [15]). In 1882, Osler presented a summary of 61 cases which had been seen in the United States, 3 of which had come under his own observation. Although nearly all of the patients in his series were immigrants, it seems noteworthy that Osler spoke of the disease as being endemic in certain parts of the United States. He wrote: "In casual visits to butcher stalls and to the shambles I have obtained six or eight large echinococci, and I have the liver of a cat with two large cysts. One of my students, Mr. A. J. Clements of Lawrence, Massachusetts, examined 270 hogs at a Montreal Abattoir and found 10 animals infected." Osler further stated, "Dr. Dean writes that a considerable proportion of the hogs in Cincinnati were at that time affected and speaks of 'whole droves,' consisting of three

or four hundred animals, all of which were diseased in this way."

The known cases of hydatid disease in the United States were reviewed by Sommer [17] (1896), who found 100 cases, and Lyon [18] (1902) collected a total of 241 cases. By 1941, Magath [15] had identified 519 cases in the United States and Canada, of which 95% were said to have occurred in immigrants. In 1953, Williams [19] presented a summary of 36 human cases believed to be indigenous to the United States. Eight of these had been found in Louisiana and five in Virginia. A year later, Magath [20] (1954) stated that about 40 indigenous cases had occurred in the United States.

The volume of medical writings on hydatid disease has, indeed, been impressive in recent years. Perhaps it is for this reason that some of the statements which have appeared are contradictory or erroneous. It is difficult to account for the statement made by Atlas and Kamenear [21] (1952): "It has been categorically stated that echinococcal disease is always contracted outside of the continental limits of the United States. All cases in the literature confirm this axiom." This statement is amply refuted by the evidence at hand.

Fig. 1.—Adult Echinococcus granulosus obtained from experimentally infected dog. Reduced 35% from mag. about × 600. Specimen courtesy of W. F. Hutchison, Department of Preventive Medicine, University of Mississippi School of Medicine.

Morphology and Life Cycle

The dog tapeworm, E. granulosus, is the smallest parasitic cestode. It inhabits the small intestine of the dog and certain other carnivorous animals, deeply imbedded in the mucous membrane.

The adult worm measures 4-6 mm. in length and in the living state shows a remarkable degree of contractility. We have seen it alter its length from more than 6 to less than 3 mm. by the process of longitudinal contraction and extension. Attachment to the host is provided by four suckers and by two rows of hooklets varying in number from about 28 to 40. The worm is composed of four segments: a head and neck, an immature proglottid, a mature proglottid, and a gravid proglottid (Fig. 1). The terminal segment is the largest, and when ripe its uterus is distended with ova. The gravid proglottid may burst, liberating ova into the lumen of the intestine, but frequently it becomes detached from the worm and is passed intact in the feces. Whether an individual worm is capable of producing one gravid proglottid after another in sequence, as they become detached, or whether it can produce only one in its lifetime is as yet unknown. Estimates vary on the time required for the worm to reach maturity, but it is probably about six to nine weeks. Jidejian [2] (1957) states, "Its life span is five months, after which it dies." This is in general agreement with the findings of Hutchison [23] (1958), but Yamashita et al.[22] (1956) describe worms from dogs which they had infected experimentally 375 days previously.

The ova are singularly resistant to changes in moisture, temperature, and light and may remain viable for months or even years (Fig. 2). When swallowed by hogs, sheep, cattle, or man, the protective membrane of

Fig. 2.—Ovum of Echinococcus granulosus in feces of infected dog. Reduced 10% from mag. about × 1,500.

the ovum is dissolved by the digestive jucies and the embryo penetrates the intestinal wall, to be swept into the portal circulation. Once it is in the blood stream it is subject to filtration by any capillary bed. The liver is therefore the most commonly involved site, with the lungs being the next most likely organ (Fig. 3). The life cycle is completed when infected viscera containing the larval stage (hydatid sand) are eaten by wild or domestic carnivores, especially the dog, wolf, and jackal, in which the worm reaches maturity in the small intestine.

Only a few instances of the natural occurrence of E. granulosus in dogs have been recorded in the United States. There has been much speculation (Osler,[16] 1882, and others) on the high incidence of natural infections with the larval stage in pigs, sheep, and, more recently, in man, while the reported incidence in dogs remains exceedingly low. Attempts to find other important definitive hosts have, however, met with failure. According to Hutchison[23] (1958), 11 natural infections in the dog have been observed in the United States.

Fig. 3.—Natural infection of Echinococcus granulosus in liver of a hog.

The first of these was noted in Washington, D. C., in 1891. Five of the eleven dogs were found in Mississippi. The actual number of dogs harboring this parasite must be considerably greater than is apparent from these reports. The parasite is so small and imbeds itself so deeply into the mucous membrane of the small intestine that it is frequently overlooked. In our experience the worm is exceedingly difficult to find even when carefully searched for in animals that have been infected experimentally.

Reported Cases

Four cases of hydatid disease have been reported in humans who were or had been residents of the State of Mississippi (Table). One of these was reported from New Orleans (Case 1). Two additional cases (Cases 3 and 4) were reported from Memphis, in persons who had been born in Mississippi but who subsequently moved to Tennessee. The locality in which they became infected could not be determined.

Case 1.—Sawitz[24] (1938) described "a case of Echinococcus cyst of the liver in a white woman, 64 years of age, a native of Mississippi," who came to autopsy at Charity Hospital, in New Orleans. No information was given as to her place of residence in Mississippi or whether she had spent any appreciable time outside of Mississippi.

Case 2.—Johnston and Twente[25] (1952) resected the apicoposterior segment of the left upper lobe of a 25-year-old Negro woman because of an undiagnosed circumscribed lesion, which proved to be an Echinococcus cyst. The patient's convalescence and subsequent course were uneventful. It was established that this patient had never been out of the state of Mississippi prior to her illness. She was a resident of Canton, a small town near the geographic center of the state.

Case 3.—Finck and Hunninen[26] (1954) reported a case of hydatid disease in a Negro man, 65 years of age, who had been born in Mississippi and who lived for the first 21 years of his life in this state. He then moved to Tennessee and spent the rest of his life in Collierville and Memphis, where he died of heart failure. "At necropsy one firm nodule, two centimeters in size, was found on the surface under the capsule in the left lobe of the liver." The lesion proved to be echinococcic.

Case 4.—Finck and Hunninen[26] (1954) also reported a case of hydatid disease in an 18-year-old Negro girl, who had been born in Mississippi but at the age of five had moved to Memphis, where she lived and met death violently. "At necropsy one cyst, 6×3.5 centimeters in size, was found in the right lobe of the liver."

Human Cases of Hydatid Disease in Mississippi

Case	Observer	Year	Race	Reported	Unreported	Sex	Age	Site Involved	Residence
1	Sawitz	1938	W	+		F	64	Liver	"Native of Miss." (?)
2	Johnston & Twente	1952	N	+		F	25	Lung	Canton, Miss. *
3	Finck & Hunninen	1954	N	+		M	65	Liver	Miss.-Tenn.
4	Finck & Hunninen	1954	N	+		F	18	Liver	Miss.-Tenn.
5	Moore	1939	N		+	F	"Young"	Liver	"North Miss." (?)
6	Carr	1955	W		+	M	9	Lung	New Albany, Miss. *
7	Webb	1958	N		+	F	37	Liver	Vaughn, Miss. *

* These patients had never been out of Mississippi. In addition, Case 1 may have had no other residence. Also, Case 5 was described as "a life-long" resident of north central Mississippi, but it could not be established that she had never been out of the state. Reports of 3 additional cases in Mississippi have been received, but confirmation and details are lacking.

Unreported Cases

We have been able to collect the following cases.

CASE 5.—In 1939, a small cyst of the liver was submitted to Dr. R. M. Moore,[27] of the Department of Pathology at the University Medical School, Oxford, Miss. The specimen was obtained as an incidental finding at laparotomy in a young Negro woman of Oxford. Microscopic examination confirmed the diagnosis of Echinococcus cyst of the liver. While it is not possible to establish the fact that this patient had never been out of the state, she had been a life-long resident of north-central Mississippi.

CASE 6.—In May, 1955, Dr. Duane Carr,[28] of Memphis, treated a 9-year-old white boy with an "abscess" in the lower lobe of the right lung. A right lower lobectomy was performed, and the abscess proved to be an infected Echinococcus cyst of the lung. This patient, a resident of New Albany, Miss., had never been outside the state prior to the onset of his illness.

CASE 7.—This was a 37-year-old Negro woman who had been treated for pulmonary tuberculosis for three years prior to her death, on Oct. 30, 1956, at the Mississippi State Sanatorium. She had been a life-long resident of Vaughn, Miss. The system review, physical examination, and laboratory data were all within normal limits, except for the far-advanced pulmonary tuberculosis. At autopsy, a well-demarcated 2.2 cm. cyst was found in the liver. The cyst wall was composed of a white soft membrane about 1 mm. in thickness,

Fig. 4.—Hydatid cyst obtained from Case 7. Note partial detachment of endocyst.

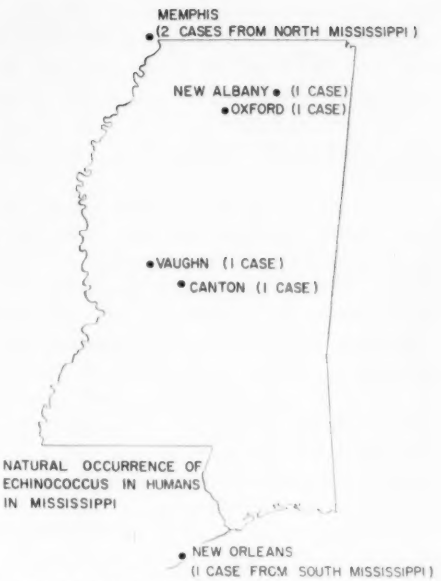

Fig. 5.—Map showing sites of human cases of hydatid disease in Mississippi.

with a second underlining more closely adherent to the liver parenchyma. Microscopic sections showed brood capsules of E. granulosus containing typical hooklets (Fig. 4).

We have received reports of two additional cases in Greenville, Miss., and one additional case in Vicksburg, Miss. We have, however, been unable to vertify these as authentic cases and can therefore mention them only as unconfirmed reports (Fig. 5).

Summary

The importance of hydatid disease in the production of human morbidity and mortality throughout most parts of the world is emphasized. Reference is made to the accumulation of data concerning its prevalence and importance in North America. Summaries are presented of three cases of hydatid infection in residents of Mississippi, none of whom had ever lived outside of this state (Cases 2, 6, and 7). Two additional cases had no known residence outside of Mississippi, but it could not be established with certainty that they had never left the state (Cases 1 and 5). In addition there

have been two cases reported from Memphis, in persons who had been born in Mississippi and who had lived for various lengths of time in this state (Cases 3 and 4). Two unconfirmed reports from Greenville, Miss., and one from Vicksburg, Miss., are also recorded.

This series of cases of human echinococcosis lends support to the previously established fact of the endemicity of this disease in the lower Mississippi valley. It now appears that infection with the dog tapeworm, Echinococcus granulosus, constitutes a significant health hazard in Mississippi, Tennessee, Louisiana, and several other southern states. This is especially true for persons engaged in farming and associated occupations, where there is close contact between man, sheep, pigs, cattle, and dogs. Attention is called to the likelihood that infections with this parasite will be seen with increasing frequency in the United States unless active programs of control are instituted.

Dr. Duane Carr and Dr. R. M. Moore gave permission to publish the cases seen by them.

Department of Preventive Medicine, The University of Mississippi School of Medicine.

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Studies on Urinary Lipase

IV. Urinary Lipase in Carcinoma of the Pancreas

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In the course of our studies on urinary lipase [1-3] we presented evidence that a fat-splitting enzyme was present regularly in the urine of man. Concentration of the enzyme ranged from 0.1 to 0.75 units, that is, 0.1 cc. to 0.75 cc. of N/20 sodium hydroxide has been required to titrate liberated fatty acids from a urine-olive oil mixture, incubated for 24 hours to a pink end-point with phenolphthalein. In patients where the values have been found elevated, that is, higher than 1.0 unit, there were symptoms or laboratory findings or both which pointed to pancreatic disease. In patients with carcinoma of the pancreas, however, values for urinary lipase were less than 1 unit. The same patients had normal values for serum and urinary diastase. The finding that the values for urinary lipase did not show any change from the normal in carcinoma of the pancreas was of no help in establishing a diagnosis, but it raised the question as to whether stimulation of pancreatic secretion with secretin might produce different values of urinary lipase in patients with carcinoma and in normal persons.

During the many years in which we have been using secretin for the evaluation of pancreatic function, the effect of the drug on serum diastase and lipase has often been examined. No noticeable change of the values for these enzymes has been found. The same is true for its effect on the concentration of diastase in the urine, but the effect of secretin on the excretion of urinary lipase seemed different. With the progress of our studies on urinary lipase, the concentration of the enzyme in the urine was also examined after injection of secretin, and it was found higher than 1 unit on many occasions in normal persons. We, therefore, started to test the urine of healthy persons and of patients free of gastrointestinal symptoms for lipase in the urine under the effect of secretin systematically.

Twenty-two persons were given secretin intravenously, and the urine was examined for its concentration of lipase before and for 24 hours or even 48 hours after the injection. The first three specimens were collected immediately before and one and two hours after the injection. Then the patients had to void about every two hours during the day and about every four hours during the night. With the injection the patients were given two glasses of water, to ascertain the excretion of urine at the wanted time. The patients were kept fasting until two hours after the drug had been

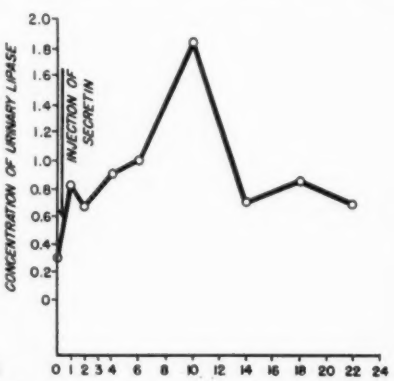

Fig. 1.—Effect of secretin on urinary lipase in a normal person.

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Supported by a grant from the Damon Runyon Memorial Fund for Cancer Research.

From the Medical and Surgical Departments of the New England Center Hospital and Tufts University Medical School.

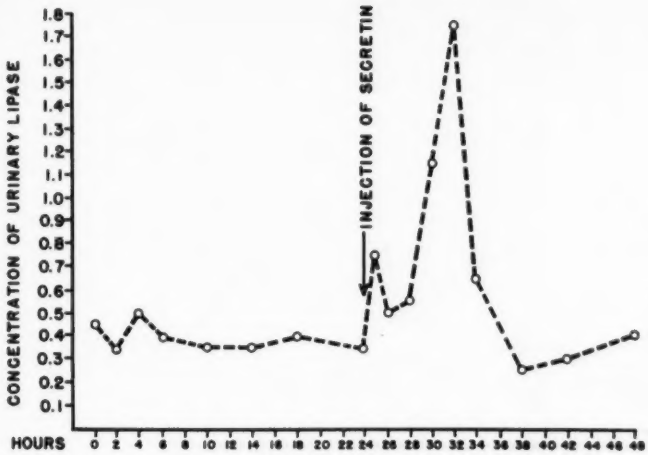

Fig. 2.—Daily fluctuations of urinary lipase and effect of injection of secretin in a healthy person.

given. The amount of secretin administered was 100 units (Lilly preparation).

Figure 1 shows the effect of secretin on urinary lipase in normals. Before the injection the value for urinary lipase is less than 0.75. About two hours after the injection it started to rise. In general the highest figures are reached after six to eight hours. In the person whose curve is demonstrated a concentration of 1.9 has been found after nine hours. But the peak may even be reached later. It is, therefore, necessary to determine the urinary lipase for a whole day in order not to miss an increase in the concentration. Twenty-four hours after the administration of the drug the values were normal again.

The daily fluctuations of the concentrations of urinary lipase are insignificant, as may be seen from Figure 2. Urinary lipase was determined about every 4 hours for 24 hours before the injection. The values recorded ranged between 0.32 and 0.5 units. After the injection the highest values, of 1.2 and 1.8 units, were reached after six and eight hours. After 10 hours the concentration of lipase in the urine was already back to the original level.

The concentration of the lipase in the urine after injection of secretin has been examined in 18 cases of pancreatic carcinoma. Figure 3 demonstrates the effect of such an injection. The urinary lipase has been examined every hour for four hours, then every second hour, and during the night every four hours. The curve shows that after injection of secretin there was a fall in the concentration of the urinary lipase. After 6 hours and after 18 hours the values dropped to 0.

The response of all 18 patients with carcinoma of the pancreas to the injection of secretin was similar to the one demonstrated in Figure 3 and completely different from the response in normal cases. There was regularly a decrease in the concentration of lipase in the urine, which in some specimens may amount to a complete disappearance of the enzyme.

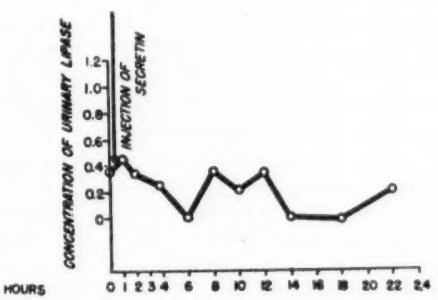

Fig. 3.—Effect of secretin on urinary lipase in a patient with carcinoma of the pancreas.

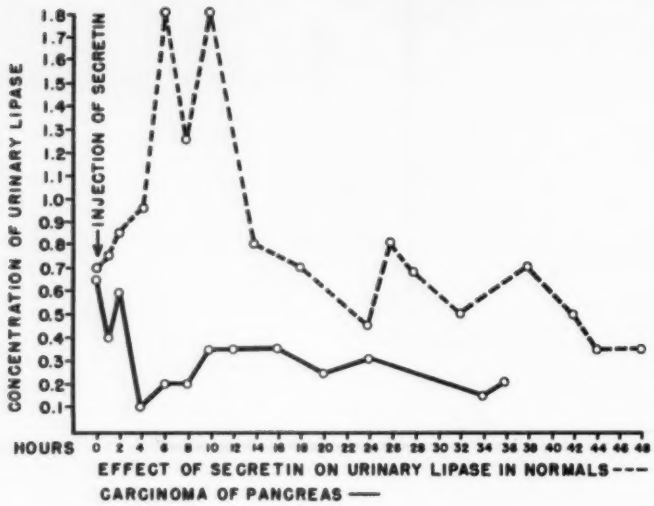
CONCENTRATION OF URINARY LIPASE
INJECTION OF SECRETIN
HOURS
EFFECT OF SECRETIN ON URINARY LIPASE IN NORMALS---
CARCINOMA OF PANCREAS —

Figure 4

Figure 4 shows the effect of secretin on the urinary lipase in a normal case and in a case of carcinoma of the pancreas where the concentration of the lipase has been examined for 48 hours after the injection in the normal case and for 36 hours in the patient with carcinoma. In the normal case the increase during the first day is followed by a marked decrease of the curve later. In six cases the course of the curve has been followed for 48 hours. The decline on the second day is more prominent when larger amounts of secretin have been given. This decrease in the amount of excreted urinary lipase is apparently an expression of a functional if transient exhaustion of the pancreas. The curve is very similar to the curve of a patient with carcinoma of the gland in the first 24 hours after the injection. We are inclined to assume that the reaction of the carcinomatous gland to secretin is an expression of an exhaustion of the organ invaded by the malignant growth.

Since the response of the pancreas of a normal person in regard to excretion of urinary lipase has been found so different from the response of a patient with carcinoma of the gland, it seemed important to us to study the effect of stimulation with secretin in cases with inflammatory processes in the gland. We have tested eight cases with recurrent pancreatitis. The curves in these patients appear definitely different from the curves recorded in normals and in patients with carcinoma. The basic levels are higher, but there is very little if any response to the injection of secretin.

Figure 5 expresses the difference of the course of the three curves. The upper curve is characteristic for the response in a normal person; the lower curve shows the course in a patient with carcinoma, and the middle curve demonstrates the curve in a patient

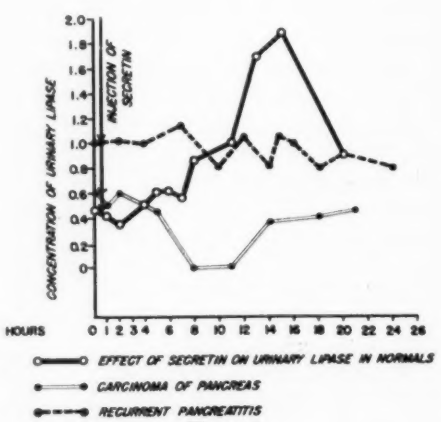

Figure 5

TABLE 1.—*Response of Urinary Lipase to Intravenous Injection of Secretin* *

Case	Before Injection of Secretin	After Injection of Secretin, Hr. 1	2	3	4	6	8	10	12	14	16	18	20	22	24
1	0.4	0.4	0.6	0.9	1.2	1.0	2.4	2.8	1.6		1.8		0.8		0.6
2	0.3	0.4	0.4	0.6	0.8	1.2	1.8	2.2	3.2		2.8		1.2		0.6
3	0.4	0.6	0.6	0.8	1.0	1.8	2.6	1.8	1.4		0.8		0.6		0.2
4	0.6	0.5	0.4	0.8	0.7	1.0	1.1	1.6	1.2		1.6		0.6		0.5
5	0.3	0.8	0.7		0.9	1.0		1.9		0.7		0.8		0.7	
6	0.3	0.8	0.5		0.6	1.2	1.8	0.7		0.2		0.3			0.4
7	0.5	0.4	0.6	0.9	0.9	0.8	2.2	2.2	1.8		0.8		0.6		0.8
8	0.3	0.6	0.4	0.8	0.8	0.6	1.8	2.2	1.6		1.2		0.4		0.4
9	0.4	0.7	0.8	1.0	1.2	0.8	2.4	1.6		0.8		0.6		0.4	0.2
10	0.6	0.8	0.6	0.8	0.9	1.6	1.4	0.8	0.4	0.8		0.5		0.4	
11	0.7	0.75	0.85	0.95		1.8	1.25	1.8		0.8		0.7			0.45
12	0.7	0.5	0.4	0.9	1.2	1.2	1.8	1.4	0.9	1.2		0.8			0.5
13	0.4	0.3	0.8	0.6	0.8	1.2	2.2	0.8	0.2	0.8		0.8			0.6
14	0.45	0.4	0.35	0.5	0.6	0.6	0.55	0.9	1.0	1.75	2.0		0.9		
15	0.4	0.95	1.0	1.4	0.5	1.6	0.45	0.05	0.45		0.5		0.45		0.5
16	0.75	0.5		0.55		1.15	1.75		0.65		0.25		0.3		0.4
17	0.4	0.5	0.7		0.8	1.25	1.8	0.9	0.8		1.05		0.5		
18	0.45	0.55	0.6		0.65	0.6	0.7	1.2	1.75		1.15		1.2		0.8
19	0.4	0.35	0.3	0.5	0.4	0.2	0.5	1.5	0.8	1.05	1.05		1.1		0.85
20	0.65	0.65	0.25		0.55		0.45	1.2	1.4		1.6	1.0			0.65
21	0.45	0.45	0.5	0.45		1.3	1.35		1.8	0.45	0.35		0.25		0.3
22	0.2	0.35	0.3	0.45	0.8	0.55	1.25	1.0	1.8	1.0		0.75		0.9	0.6

* 22 normals or cases free of gastrointestinal disorders.

with recurrent pancreatitis. The middle curve is similar to the curve in Figure 2 for the first 24 hours, which showed the daily fluctuations of the urinary lipase values in a normal person without secretin. The difference is that the curve of the patient with pancreatitis lies on a markedly higher level.

Tables 1, 2, and 3 give the complete results of the response of urinary lipase to intravenous injection in all 49 cases where the examination was performed. They include 22 patients without medical disease or gastrointestinal disorders, 18 patients with pancreatic carcinoma, and 8 patients with recurrent pancreatitis. One patient (Table 3, Case 9) suffered from Hodgkin's disease

TABLE 2.—*Response of Urinary Lipase to Intravenous Injection of Secretin in Eighteen Cases of Carcinoma of Pancreas*

Case	Before Injection of Secretin	After Injection of Secretin, Hr. 1	2	3	4	6	8	10	12	14	16	18	20	22	24
1	0.6	0.8	0.4	0	0.1	0	0.4	0.6	0.4		0.4		0.4		0.2
2	0.4	0.6	0.6	0.4	0.3	0.4	0	0.2	0.6		0.4		0.3		0.3
3	0.5	0.4	0.5	0.6	0.4	0.2	0.4	0.6	0.8		0.2		0.5		0.5
4	0.4	0.4	0.8	0.6	0	0.2	0.2	0	0.4		0.6		0.1		0.6
5	0.6	0.6	0.4	0.5	0.6	0.6	0.7	0.5	0.3		0.2		0.6		0.7
6	0.65	0.4	0.6		0.1	0.2	0.2	0.35	0.35	0.35			0.25		0.3
7	0.35	0.4	0.35		0.2	0	0.35	0.2	0.35	0.05		0			0.3
8	0.3	0.4	0.6	0.7	0.2	0.2	0.7	0.4	0.7	0.6		0.3		0.6	
9	0.6	0.8	0.6	0.5	0.4	0.6		0.2		0.3		0.5			0.4
10	0.5	0.4	0.6	0.2	0.6	0	0.4		0.6		0.2		0.4		0.3
11	0.6	0.4	0.5	0.4	0.1	0.2	0.1		0.1		0.6		0.3		0.6
12	0.5	0.6	0.8	0.6	0.4	0.6	0.8	0.3	0		0.1		0.6		0.4
13	0.6	0.5	0.6		0.45		0		0	0.4		0.5		0.6	
14	0.8	0.6	0.9	0.2		0.1	0.8		0.9	0.75		0.4			0.8
15	0.65	0.6		0		0.75			0.6	0					0.45
16	0.6	0.6	0.5	0.7		1.0	0.6	0.2		0.2		0.4		0.6	
17	0.6	0.8	0.6	0.4		0.8		0.4		0.2		0.6		0.7	
18	0.4	0.6	0.4	0.9		0.2		0.1		0.4		0.6			0.3

TABLE 3.—*Response of Urinary Lipase to Intravenous Injection of Secretin in Eight Cases of Recurrent Pancreatitis and One Case of Hodgkin's Disease with Pancreatic Involvement (Case 9)*

Case	Before Injection of Secretin	After Injection of Secretin, Hr.													
		1	2	3	4	6	8	10	12	14	16	18	20	22	24
1	1.0	1.0	1.0		0.9		1.2	0.8	1.2	0.8	1.1	1.0	0.8	0.9	0.8
2	1.1	0.9	0.8	0.9	0.9	1.7	1.0	0.9		0.9		0.9			
3	1.0	1.0	1.0	1.15	0.8	1.05		1.05		1.0		0.9		0.9	0.8
4	0.9	0.8		1.1	1.05	1.05		1.4		1.0		0.75		1.3	1.05
5	1.2	1.4		0.45	0.5	0.4		0.65		0.75		0.8		0.8	
6	1.1	1.4		1.2			1.0		1.4		0.6		0.8		0.8
7	0.8	1.2		1.0		1.1			0.8		1.0		0.6		1.1
8	1.05	1.2		1.4		0.8		1.2		1.0		1.1		0.6	
9	1.05 1.2	1.05	1.35	1.65	1.4	0.8	1.1	1.05		1.0		1.2		1.05	

with pancreatic involvement. The diagnosis was made through biopsy of pancreatic tissue after laparotomy.

Forty-nine patients were given secretin intravenously, and the concentration of the lipase in the urine was determined for 24 to 48 hours after the injection. Among those cases there were 22 with no medical disease at all or without any gastrointestinal symptoms; 18 patients had carcinoma of the pancreas; 8 suffered from recurrent pancreatitis, and 1, from Hodgkin's disease with involvement of the pancreas. In the patients free of medical disease or free of symptoms of the intestine, the concentration of the urinary lipase was less than 0.75 units before the injection of secretin. When the urinary lipase was determined several times within 24 hours before the secretin was given, the fluctuations of the concentration appeared small. In this first group the urinary lipase began to rise about two hours after the injection. The highest values were reached six to eight hours after the injection or even later. The peak of the curve in these cases showed values of 1.5 units or more. Twenty-four hours after the injection the values reached the level present before the injection or they were already even lower. In 18 cases of pancreatic carcinoma there occurred regularly a marked decrease of the concentration of urinary lipase; in some specimens the lipase disappeared completely. Seventeen of these patients were explored, and the preoperative diagnosis was confirmed through biopsy. In 10 cases the tumor was localized in the head of the gland; in 7 cases it was found in the body or tail. In the remaining case, who was not operated on because of ascites, the diagnosis was confirmed later at autopsy. From a clinical point of view it is important to note that the response to secretin did not differ in the cases with the tumors localized in the body or tail from those with the tumor in the head of the organ. In eight cases of recurrent pancreatitis there was little change of the values of urinary lipase as the result of the injection of secretin. The curve is on a markedly higher level than the curve which shows the daily fluctuations of the concentration of urinary lipase without secretin.

After injection of secretin a marked rise of the concentration of urinary lipase occurred in the 22 cases without any disease of the gastrointestinal organs; a sharp decrease of the values for urinary lipase was found in the 18 cases of carcinoma of the pancreas, and very little if any response could be demonstrated in the 8 cases of recurrent pancreatitis, with the curve running on a markedly higher level than in normal persons without secretin. The examination of the response of the pancreas to injection of secretin measured through the concentration of lipase in the urine may, therefore, be helpful in the diagnosis of carcinoma of the pancreas and in the differentiation between carcinoma and inflammatory processes in the organ.

Summary

The concentration of urinary lipase was determined for 24 hours after injection of secretin in 49 patients—22 cases without medical disease or free of gastrointestinal symptoms, 18 cases of carcinoma of the pancreas, 8 cases of recurrent pancreatitis, and 1 case of Hodgkin's disease with involvement of the pancreas.

In the persons without gastrointestinal symptoms there occurred a marked increase of the concentration of the lipase in the urine, beginning about two to four hours after injection and rising to values well beyond 1.5 units.

In the cases of carcinoma of the pancreas there was a marked decrease of the concentration of the urinary lipase. The drop in the concentration occurred in cases of carcinoma of the head as well as of the body or tail of the organ.

In eight cases of recurrent pancreatitis there was little if any response of the concentration of urinary lipase to the injection of secretin. The curve in recurrent pancreatitis showed insignificant fluctuations but on a markedly higher level than the daily fluctuation of the urinary lipase in normal persons without secretin. The curve of the patient with Hodgkin's disease resembles the curve of the patients with recurrent pancreatitis.

The examination of the urinary lipase after injection of secretin may be helpful in the early diagnosis of the carcinoma of the pancreas.

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Adult Hypertrophic Pyloric Stenosis

Report of Two Cases with Variable X-Ray Findings

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Hypertrophic pyloric stenosis is not a very rare condition in the adult.[1] Although this lesion is much more prevalent during infancy (1 in 150 male infants in Sweden),[2] it occurs often enough in adult life to warrant consideration in our differential of upper gastrointestinal symptomatology.

Jean Cruveilhier first described adult hypertrophic stenosis in a 72-year-old woman, in 1892.[3] Maier published a series of 31 adult cases, in 1885, all of whom had a history of symptoms in infancy suggestive of the congenital type of lesion.[4] In 1928, Crohn concluded that very few of the adult cases had a congenital basis.[5] Some investigators have considered the symptomatology and radiologic findings to be sufficiently characteristic to allow a clinical diagnosis of the entity.[6]

The purpose of this paper is to present two cases of adult hypertrophic pyloric stenosis, one focal, the other diffuse, in which the symptoms and radiologic findings were sufficiently variable to prevent a definitive diagnosis without exploratory surgery.

Report of Cases

Case 1.—A 50-year-old white male pastry cook was admitted to Mount Carmel Mercy Hospital, on March 6, 1955, with a complaint of an upset stomach. The patient stated that a year prior to admission he had begun to experience daily epigastric fullness and slight pain, described as feeling like "being tied in knots." The symptoms occurred between two and three hours after heavy meals, lasting one to two hours, and were occasionally accompanied by a dull, burning interscapular pain. During this same interval, the patient had sustained a 6 lb. weight loss. He had no loss in appetite, nausea, vomiting, heartburn, or melena. Black stools had been noted on rare occasions, which he attributed to the ingestion of an iron preparation prescribed by his physician. Repeated upper gastrointestinal x-rays had shown a "gastric ulcer," for which an ulcer diet had been prescribed. The patient had noted a marked relief of symptoms since the initiation of the ulcer regimen.

For a week prior to admission the patient had experienced a sharp pain in the right shoulder, aggravated by motion of the right arm. The past history was noncontributory.

Physical examination at the time of admission revealed a well-developed, well-nourished white man in no distress. The only abnormal physical findings were limited to the right shoulder, where point tenderness was elicited over the supraspinatus muscle to palpation.

Laboratory tests revealed a normal urinalysis and c. b. c. The prothrombin time was 15 seconds (100%). The serologic test for syphilis (Kline exclusion) was negative. The N. P. N. was 28 mg. %. Gastric analysis disclosed 5 degrees of free and 25 degrees of total acid in the fasting state and 10 degrees of free and 19 degrees of total acid at one hour after histamine stimulation. There was a trace of occult blood in two of the analysis specimens.

Radiologic examinations, including repeated upper gastrointestinal series, had disclosed a persistent narrowing of the prepyloric stomach, which changed slightly in contour with peristalsis, along with a slight irregularity adjacent to the narrowed segment, interpreted as an ulcer crater. At no time did the stomach show evidence of prolonged retention of contrast media (Fig. 1).

Hospital Course.—The admitting diagnosis was a gastric ulcer, with malignancy to be ruled out.

On March 8, 1955, the patient underwent an exploratory laparotomy under thiopental (Pentothal) and nitrous oxide-oxygen-ether anesthesia. The stomach disclosed a tumor mass of walnut size in the region of the pylorus, along with a few soft nodes in the gastrocolic ligament. The duodenum was freely mobile and revealed no evidence of ulceration or scarring. It was decided at this time to submit the tumor mass for pathologic examination. A wedge resection was carried out. Although the gross appearance of the tumor was compatible

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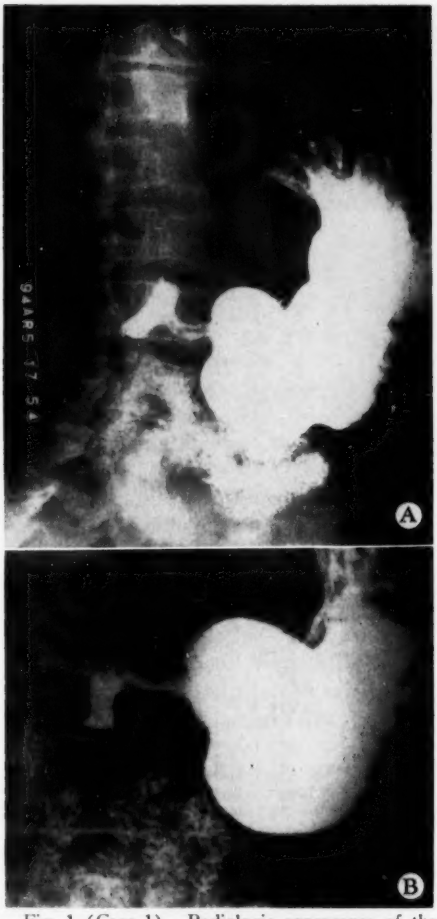


Fig. 1 (Case 1).—Radiologic appearance of the stomach and pyloric canal. *A*, abrupt narrowing of the pyloric canal is contrasted with the well-distended gastric antrum and the regular smooth contour of the stomach proximal to the pyloric defect. *B*, a smooth crescentic invagination of the base of the duodenal bulb (Kirklin sign) and straight mucosal folds within the elongated pyloric canal suggest hypertrophic pyloric stenosis.

with a malignancy, microscopic examinaton failed to show any malignant characteristics. A 50% gastric resection and a Billroth I type of anastomosis were carried out. The patient withstood the procedure well, had an uneventful postoperative course, and was discharged from the hospital on the ninth postoperative day.

Pathologic Report.—Grossly, the specimen consisted of a portion of stomach measuring 16 cm. in length and 7 cm. in greatest width. The serosa and mucosa were intact. The distal portion of the specimen revealed a palpable mass measuring 5 cm. in length, 4 cm. in width, and 2 cm. in greatest thickness. Cut section revealed a marked hypertrophy of the muscular wall, which had a woody consistency. Microscopically there was tremendous hypertrophy of the muscular coats of the stomach in the region of the described tumor (Fig. 2). The general architecture of the tissue was preserved, but the individual muscle fibers varied from 2 to 10 times normal size. Although there was no evidence of ulceration, there was a slight chronic inflammatory process involving the gastric wall. The final diagnosis was idiopathic hypertrophy of the pylorus.

CASE 2.—A 67-year-old white housewife was admitted to Mount Carmel Mercy Hospital, on Oct. 21, 1958, with a complaint of intermittent nausea for one and one-half years' duration. She stated that the nausea was often precipitated by meals and accompanied by excessive eructation and occasionally associated with a vague epigastric discomfort. The patient had experienced no vomiting, weight loss, heartburn, melena, or change in bowel habits. Because of her symptoms, she consulted her physician, who obtained upper gastrointestinal x-rays that repeatedly disclosed a "mass in the stomach" (Fig. 3). An attempted gastroscopic examination did not further delineate the nature of the mass.

Medical History.—The patient had had an appendectomy and right oophorectomy at age 27 years and a right radical mastectomy "for cancer" at age 37 years.

The review of systems and family history were noncontributory.

The pertinent physical finding was a surgical absence of the right breast.

Laboratory tests revealed a hemoglobin of 13.8 gm. and a normal white blood cell count, with a normal differential. The urinalysis was within normal limits. The serologic test (Kline exclusion) for syphilis was negative. An erythrocyte sedimentation rate was 7 mm. in one hour. The "C"-reactive protein was negative. An electrocardiogram was within normal limits. An x-ray of the chest at the time of admission showed an absent right breast, without other thoracic or pulmonary abnormalities.

Course in Hospital.—A surgical consultant felt an exploratory laparotomy was indicated. On Oct. 10, 1958, under thiopental sodium and cyclopropane anesthesia, surgery was performed. Palpation revealed a soft tumefactive process in the prepyloric region of the stomach on the lesser curvature. There were numerous adhesions over this area of the pylorus, extending to the liver and gastrohepatic omentum. A 60% gastric resection with Billroth II anastomosis was carried out. The patient tolerated the procedure well, made an un-

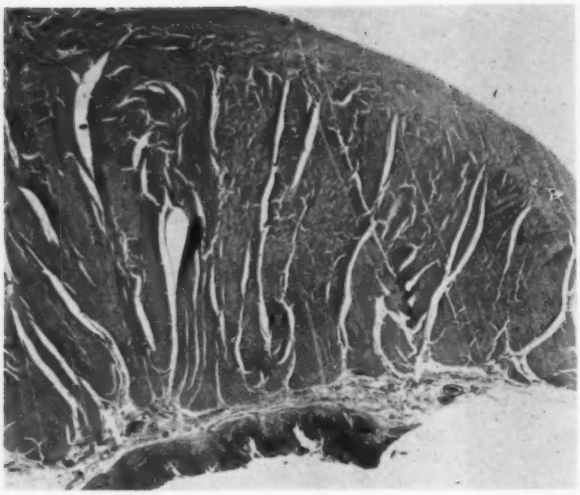


Fig. 2 (Case 1).—A low-power photomicrograph of a longitudinal section of the pyloric canal, showing hypertrophied musculature overlying the intact mucosa and the normal thickness of the circular muscle coat in the region of the gastric antrum (right side of slide). Hematoxylin and eosin stain.

eventful recovery, and was discharged from the hospital on the seventh postoperative day.

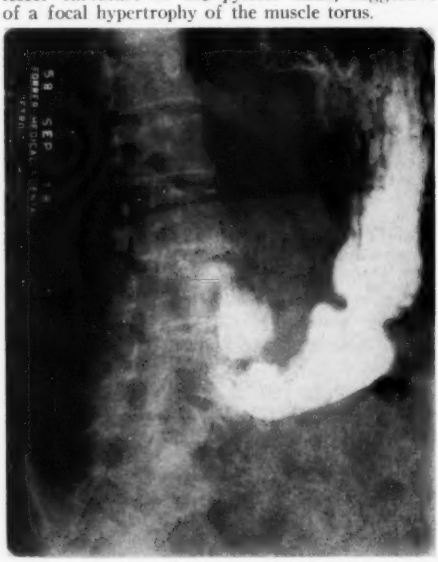
Pathologic Report.—The specimen consisted of a portion of stomach measuring 16 cm. in length, 9 cm. in greatest transverse diameter, and from 0.5 to 1 cm. in thickness. The serosa and mucosa were intact. There was a thickening in the region of the pylorus, with a complete absence of rugal folds in the distal one-third of the specimen. Microscopically, a marked hypertrophy and hyperplasia of the smooth muscle of the stomach was present, without evidence of infection, ulceration, or neoplasia.

Comment

The etiology of adult hypertrophic pyloric stenosis, like its congenital counterpart, remains obscure. Some investigators suggest a familial inheritance of the entity, citing the 80% male incidence as in the congenital type and the reported cases occurring in parents and siblings as substantiation for this contention.[7-9] Bockus, in his clinical classification of the entity, includes one group with gastrointestinal symptoms since childhood.[4] Others point out the persistence of a "pyloric tumor" for years after the symptomatic period of infancy. In infants treated for congenital hypertrophic pyloric stenosis by gastroenterostomy and operated on for other reasons in later life, Belding and Kernohan demonstrated a persistent pyloric hypertrophy.[10] In one series, in which antispasmodics and diet were used as definitive therapy, Runström was able to show a persistent pyloric defect for many years.[11]

A neurogenic imbalance has been proposed as the cause for hypertrophic pyloric stenosis in both infancy and adult life. Based on the experimental work of Inger-

Fig. 3 (Case 2).—Radiologic appearance of the stomach, showing a persistent filling defect on the lesser curvature of the pyloric canal, suggestive of a focal hypertrophy of the muscle torus.



soll,[12] in which he produced pathologic changes in the pyloric myenteric ganglion cells of rats with prolonged vagal stimulation, Belding and Kernohan demonstrated degenerative changes microscopically in the pyloric ganglia cells of both infants and adults.[10] Raia and co-workers considered the pathologic changes in the myenteric plexuses to be reversible in the infant and irreversible in the adult cases of hypertrophic pyloric stenosis.[13] That an abnormal vagotonic state existed in infancy and was possibly etiologic in pyloric stenosis was suggested by Bendix and Necheles, who for years followed a series of infants operated on, demonstrating a high incidence of peptic ulceration and other gastrointestinal disorders.[14]

Finally, the personality pattern of adults with hypertrophic pyloric stenosis has been implicated as being etiologic. Berk and Dunlap reported two cases in which somatic symptoms were markedly aggravated by distressing economic and domestic situations.[15]

The type and extent of pyloric hypertrophy correlates with the structural anatomy of the circular musculature of the pyloric canal. Cunningham and Wernstedt have demonstrated that the pyloric canal in man contains a specialized structure of circular muscle fibers, consisting of two sphincter loops (Fig. 4). A proximal sphincter obliquely encircles the proximal end of the pyloric canal and the distal sphincter, representing a thickening of circular fibers corresponding to the gastric portion of the pyloric sphincter. These two sphincter loops converge on the lesser curvature of the pyloric canal to form a muscular prominence, the muscle torus.[16] Where muscle hypertrophy is focal in nature, it is often found to involve the region of the muscle torus.[17] Symptomatology with this type of lesion is often absent or mild, owing to a lessening of obstructive complications. By contrast radiologic studies, filling defects and indentations in the pyloric region are found.[16] Where the pyloric hypertrophy is more diffuse, involving both sphincter loops and the interposing muscle fibers, the degree of obstruction and symptoms are more pronounced. Whether the focal form of hypertrophy represents the early stage of diffuse hypertrophy or persists as a separate entity is not known.[16]

The symptoms and signs of hypertrophic pyloric stenosis are more characteristic in infancy than adult life. Yet any series of infants operated on with this tentative diagnosis will reveal other conditions in 5% to 10% of cases.[18] At an adult level, many benign and malignant entities could produce symptoms and physical and radiologic findings similar to those in hypertrophic pyloric stenosis. Anorexia, early satiety with meals, upper abdominal distention with pain aggravated by eating, post-

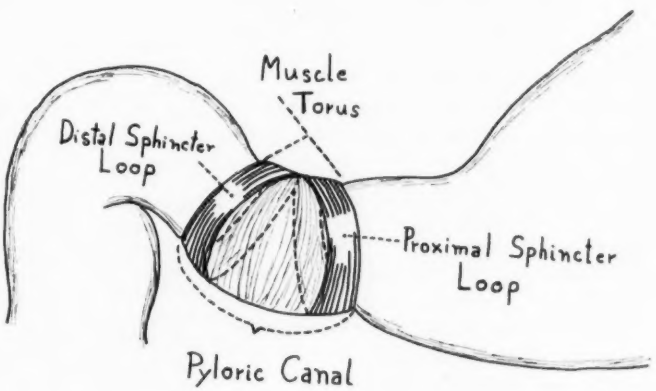


Fig. 4.—Normal structural anatomy of the circular muscle coat of the pyloric canal. Note the proximal and distal sphincter loops converging on the lesser curvature to form the muscle torus. (Drawn after Skoryna, Dolan, and Gley.[16])

prandial vomiting, and weight loss are not symptoms characteristic enough to differentiate lesions in the pyloric or duodenal regions.[3,19]

By barium meal x-ray study, an abrupt narrowing of the pyloric canal in contrast to a well-distended gastric antrum seems to be a constant feature.[16] A smooth, regular contour of the stomach proximal to the pyloric defect, along with regular straight mucosal folds in the pylorus, indicates lack of mucosal involvement with the lesion.[15] Elongation and fixation of the pyloric canal, the "pyloric string sign," and a smooth crescentic invagination of the base of the duodenal bulb, as described by Kirklin, though suggestive of hypertrophic pyloric stenosis, are not diagnostic of the lesion.[3,16] Indentations, filling defects, and barium projections are observed in focal hypertrophy of the torus or other segment of the circular musculature.[16]

A pyloric ulcer with cicatrization, an encircling myoma, a gastric malignancy or eosinophilic granuloma, pancreatic anomalies, or tumors with secondary gastric involvement would have to be considered in the differential diagnosis of a chronic partial pyloric obstruction in the adult.[3,19,21]

The incidence and relative significance of associated gastrointestinal lesions with hypertrophic pyloric stenosis is controversial. Some have reported a high incidence of complicating ulcers, mucosal inflammatory changes, and other intra-abdominal lesions with pyloric stenosis.[3,15,19,20] Bockus considers the presence of a pyloric ulcer or significant gastritis as excluding the diagnosis.[4] Others admit a relationship between gastric or duodenal ulcers and hypertrophic pyloric stenosis but do not know their etiologic significance.[19] Kleitsch considers associated gastric ulcerations to be secondary to stagnation of stomach contents and a lack of acid neutralization by the reflux of duodenal secretions. Ulcerations within the fixed, stenotic canal, because of their longitudinal axis to the pylorus, and superficial character, are considered to be traumatic in etiology. Finally, duodenal ulcers are thought to represent distinct and separate pathologic processes.[6]

There is general agreement that the treatment of hypertrophic pyloric stenosis is surgical. In the absence of peptic ulcerations, the surgery would be that for simple pyloric obstruction.[6] Gastroenterostomy or pyloric sphincterotomy are considered adequate corrective procedures, but neither affords tissue for a pathologic confirmation of the diagnosis.[4,6,19] Only temporary relief, necessitating reoperation, has been reported by McCann and Dean.[22] Stomal ulcers, duodenal diverticula, or late pyloric cicatrization exist as possible sequelae of the above procedures.[1] With evidence of existing or past gastric or duodenal ulceration, the surgery should be an adequate gastrectomy.[6]

Summary

Two cases with operation for adult hypertrophic stenosis with variable radiologic findings are reported. In one the symptomatology was attributed to a peptic ulcer for over a year. Both were operated on, with a suspicion that a gastric malignancy might be the underlying cause of the symptoms and radiologic findings. A subtotal gastrectomy was tolerated well by both patients and appeared to be curative.

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Eosinophilic Granuloma Confined to the Lung

Report of a Case

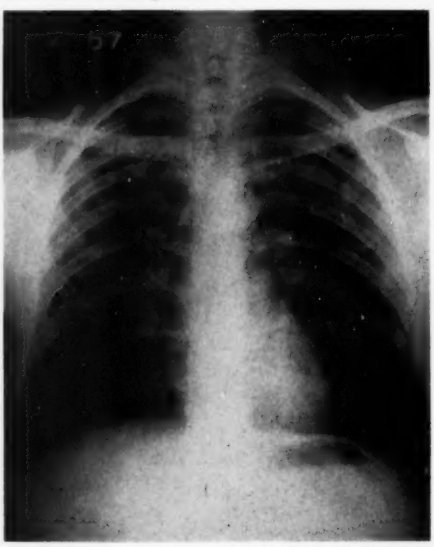
CAPT. CHRIS L. MENGIS (MC), U. S. Army

Of possible etiologic significance with regard to pulmonary fibrosis of unknown cause is the small spate of cases of pulmonary histiocytosis without evidence of systemic spread reported since 1952. Of the 17 cases found in a review of the current literature, 14 were reported from military or Veterans Administration hospitals—5 from the same institution. All were diagnosed by lung biopsy. Rather than an occupational disease of military service, this is probably a reflection of the necessity for a definitive diagnosis for disposition. The following material is the description of a further case followed for 22 months.

A 28-year-old man was admitted to the U. S. Army Hospital, Fort Jay, on Feb. 21, 1957, because of abnormal findings on a routine separation chest x-ray. His chest film on entrance into the service in March, 1955, was normal. Past history revealed an attack of "virus pneumonia" in April of that year. Two chest films taken during this illness could not be located. For five months prior to the present admission, the patient had a morning cough productive of a teaspoon of yellow phlegm, which, during the last month prior to hospitalization, had been streaked with blood on a few occasions. He had felt well, had experienced no night sweats, and had gained approximately 9 lb. over the previous five months. There had been no known exposure to tuberculosis or potentially hazardous industrial environment. Physical examination of this well-nourished muscular man was not remarkable, except for enlargement and pitting of the tonsils and considerable anterior cervical and axillary shotty adenopathy. The lungs were clear to percussion and auscultation. Ancillary studies included numerous normal white cell counts with occasionally a slight lymphocytosis but never eosinophilia; sedimentation rates ranged from 17-20 mm. (Wintrobe), with normal hematocrits, and urinalyses were normal. A coccidioidin skin test was negative, but P. P. D. No. 2 and histoplasmin were positive. Three 24-hour sputum collections failed to yield acid-fast bacilli on either smear or culture. Collodion-agglutination and complement-fixation tests for histoplasmosis were negative, as were complement-fixation tests for blastomycosis and coccidioidomycosis. No bacterial or fungal pathogens were recovered from the sputum. The chest x-ray revealed a bizarre reticulated infiltrate in the upper two-thirds of each lung field, sparing the hila, which did not change significantly on interval films during hospitalization to September, 1957. A Vim-Silverman needle biopsy of the liver revealed normal hepatic tissue. A biopsy of one of the larger right scalene nodes in March, 1957, revealed only reactive hyperplasia. No fungi or acid-fast bacilli were recovered from the tissue. No skeletal lesions were found on complete bone survey in September, 1957. The electrocardiogram was normal.

During his hospitalization, the patient remained well. His morning cough subsided. Pulmonary-

Fig. 1.—Admission film, demonstrating diffuse reticulonodular disease confined to the upper two-thirds of both lung fields.



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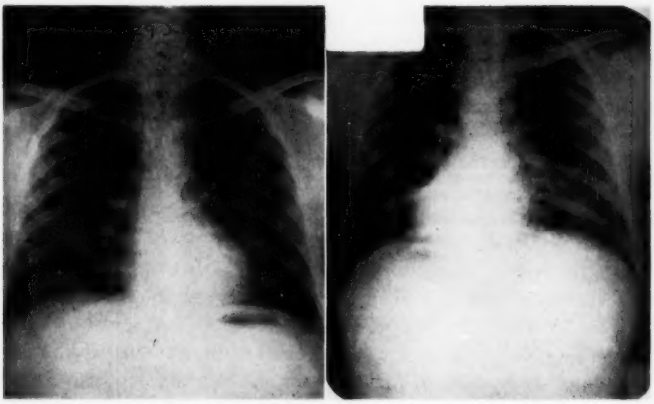

Figs. 2 and 3.—Interval film of July, 1957, and December, 1958, demonstrating absence of significant change.

function studies were undertaken in April, 1957, the maximum breathing capacity, vital capacity, and timed vital capacity all being normal. A lung biopsy was performed on May 14, 1957, through a 3½ in. incision in the fourth left intercostal space anteriorly. Inspection and palpation of the lung surface in this area revealed several small nodules, one of which was excised as a small wedge for microscopic examination. The specimen was a portion of the lung parenchyma measuring 1.5 cm. across and 13 mm. in thickness, and it was covered on one surface by pleura. Just subpleurally and within the lung parenchyma there was a 0.4 cm. firm circumscribed white mass. Microscopically, there appeared in the pulmonary parenchyma a granulomatous process, consisting of histiocytes,

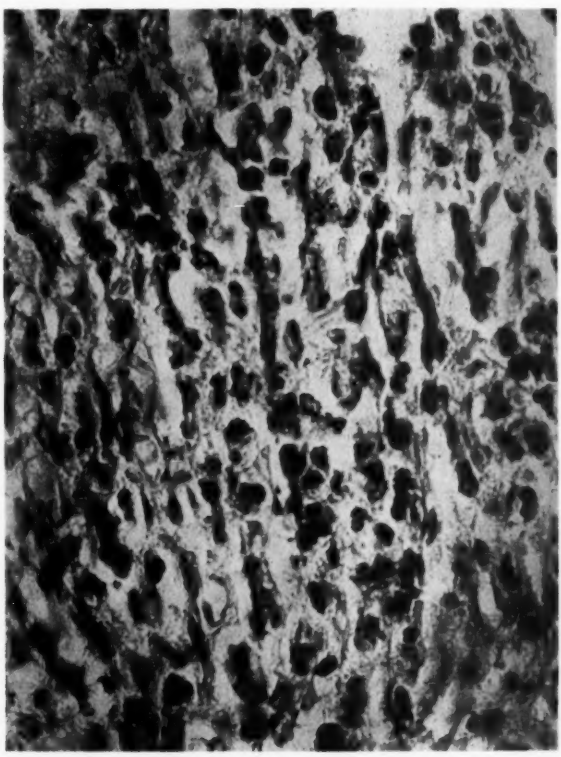

Fig. 4. — Photomicrograph of lung biopsy. Sheets of foamy histiocytic cells infiltrated with eosinophils and round cells.

fibroblasts, occasional eosinophils, lymphocytes, and neutrophils. The wall of a terminal bronchiole was seen to be markedly thickened, with, in some areas, invasion by eosinophils and lymphocytes and disruption of the normal architecture. Large multinucleated giant cells were seen on the endothelial surface. A small vessel, apparently an artery, was almost occluded by the granulomatous process. Histologic diagnosis of eosinophilic granuloma was confirmed by Dr. Sadao Otani and concurred in by the Armed Forces Institute of Pathology.

The patient was placed on prednisolone, 80 mg. a day, in July, 1957, and remained on this dosage for three weeks, after which he continued to receive 20 mg. a day for six weeks. Typical "moon face" of Cushing's syndrome developed. No change was noted in chest films to Sept. 30, 1957, when he was separated from the army. Since then he has continued to work as an applications engineer, traveling a large area, remaining fit, though he has a slight cough and noted slight shortness of breath while swimming this past summer. There has been no change in the urinary output. The chest x-ray of December, 1958, reveals no further change.

Comment

Otani and Ehrlich [9] and Lichtenstein and Jaffe [5] simultaneously reported benign granulomas of bone in 1940, the eponym "eosinophilic granuloma" being coined by the latter authors. With the passage of time, it became apparent that the disease involved also lung tissue, skin, lymph nodes, the pituitary, and other organs, and many cases originally classified as eosinophilic granuloma were found to assume characteristics of the more fulminant nonlipid reticuloendothelioses, Hand-Schüller-Christian disease and Letterer-Siwe disease. In 1953, Lichtenstein suggested the group be labeled more aptly "Histiocytosis X," the X referring to the unknown etiology of the histiocytic reaction.[6] Of a total of about 200 cases of eosinophilic granuloma, Thompson et al.[11] found in the literature 39 cases with pulmonary involvement, but only 5 of these were isolated to the lung, and in only 12 of the 39 was it necessary to resort to lung biopsy to obtain tissue confirmation. A subsequent follow-up of these cases was inadequate, varying from two and one-half months to six years. Three patients progressed to an early death. Of 29 others in whom clinical course was reported, 16 had improvement or complete recovery, 11 were unchanged (including 1 followed for six years), and 2 had progressive disease. Moderate or marked improvement was seen in three cases receiving irradiation, three treated with steroids, one with streptomycin, one with lung resection, and three with no therapy.

Symptoms ascribed to the disease include nonproductive cough in half of the cases; weight loss, chest pain, and manifestations of diabetes insipidus, each in about a third; dyspnea in a quarter, and also weakness, fatigue, night sweats, hemoptysis, skeletal discomfort, and spontaneous pneumothorax.

In 1951, Farinacci et al.[3] first described two cases of eosinophilic granuloma of the lungs with no evidence of extrapulmonary foci. Of the 18 cases of isolated pulmonary histiocytosis herein accumulated, age ranged from 15 to 59, but 14 patients were between 20 and 35 years of age. All but one were men and, of the 13 in whom race was noted, 12 were white. They were followed from 3 months to 28 months after the first positive x-ray, the average being 12 months. Eight manifested positive tuberculin skin tests; six reacted to histoplasmin and two to coccidioidin. All had negative skeletal surveys, and none had increased urinary output when first seen. The patient reported by Weiss and Johnston,[13] however, developed diabetes insipidus a year after diagnosis, and one of Auld's cases developed a skin rash, manifested histologically by infiltration with histiocytes, after being given steroid therapy.[2] Symptoms were similar to those of the disseminated group. Fourteen had a dry or nonproductive cough from two months to three years prior to being seen. Weight loss, usually small, was reported in eight; mild exertional dyspnea, in three; increased fatigability, in two; skeletal pain, in three, and fever and sweats, each, in one. Physical examination was not remarkable in 14 cases. Right pneumothorax was pres-

ent in two, scattered wheezes in one, and scattered rales in a fourth. Five were noted to have a mild blood eosinophilia at one time or another. Of seven patients in whom albumin-globulin ratio was reported, three had increased globulin. Eight were subjected to a scalene node biopsy, in all of which the nodes were either normal or showed only reactive hyperplasia. Six sternal marrow aspirations were performed, all normal, as were two needle liver biopsies and three bronchoscopic examinations. Chest x-rays all revealed a reticulonodular appearance, with "honey-combed" background, commonest in the upper two-thirds of the lung fields.

Steroid therapy of various sorts and dosages was administered to nine patients, including our own, who received sufficient prednisolone to cause him to become "moon-faced" for two months. Five, including our case, evinced no change on serial chest films. Of the other four, x-rays improved in one who received moderately large doses of repository corticotropin injection (ACTH Gel) and cortisone for 16 days, in another who received moderate doses of prednisone (Meticorten) for 115 days, and in a third who cleared after three months of prednisone therapy. Livingston's patient remained unchanged for six months on prednisone therapy, then rapidly cleared.[7]

The nine other patients were variously handled. Three who received streptomycin, aminosalicylic acid (PAS) and isoniazid (INH) for reasonable lengths of time failed to improve. Four received no therapy at all and x-rays were unchanged, except for one in whom temporary clearing was noted following thoracotomy. Improvement after thoracotomy was also noted in two of the cases who had previously failed to respond to antituberculous chemotherapy. X-ray therapy was administered to three patients, one of whom also received steroids, without appreciable change. Radiologic improvement consisted generally in diminution of the size and number of nodulations, leaving residual fibrotic strands.

The lungs were described at the time of thoracotomy as containing small gray or whitish-gray nodules visible or palpable beneath the pleural surface. Microscopically, nodular infiltrations of histiocytes and eosinophils were seen, along with diffuse thickening of the alveolar walls by fibrosis or cellular infiltrate. Lymphocytes, plasmacytes, and neutrophils were variously reported as infiltrating into these areas, and in several instances macrophages laden with brown pigment were noted.[2,3] Whether cavitation in the nodule eventuates from evacuation of the central necrotic area into bronchioles or is the result of a central cleft or stellate defect, as suggested by Arnett and Schulz,[1] is not clear.

This type of granulomatous disease does appear, however, to be related to pulmonary fibrosis. Because symptoms are minimal or absent, diagnosis in the general population is not likely unless routine survey films of adults are accomplished. The true incidence of pulmonary histiocytosis, as mirrored by the growing number of microscopically substantiated case reports, is probably larger than previously realized, although not nearly so large as the number of cases of pulmonary fibrosis of unknown etiology.

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Convulsive Equivalent States

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Introduction

The number of terms applied to this disorder is exceeded only by the numerous and widespread symptoms and signs that the illness may manifest. In the medical literature, the condition has been described under the following titles: abdominal epilepsy,[2] paroxysmal abdominal pain,[3,4] hypothalamic and thalamic epilepsy,[5] masked epilepsy,[6] the periodic syndrome,[7] visceral epilepsy,[11] diencephalic autonomic epilepsy,[8] and diencephalic autonomic discharge.[9] The term convulsive equivalent state[1] signifies a paroxysmal cerebral dysrhythmia manifested clinically by symptoms in various organ systems. Convulsive movements and loss of consciousness need not be present.[1] Of interest to internists are such symptoms as paroxysmal abdominal pain, hypertension, nausea, vomiting, fever, borborygmi and belching, flushing, blanching, cyanosis, urinary incontinence, syncope, and migraine headaches.[1,3-5,7,10-19] The paroxysmal nature of the symptoms is the clue to this diagnosis and should lead to a request for an electroencephalogram. Among several patterns that may be noted, the occurrence of 14- and 6-per-second positive spikes obtained during sleep may be especially indicative of a convulsive equivalent or epileptic equivalent state. In 1951, Gibbs and Gibbs called attention to this pattern which was found in the tracings of about 6% of epileptics and about 2% of normals.[5] Poser and Ziegler reported a total of 136 patients whose sleep electroencephalograms showed the 14- and 6-per-second positive spike complexes.[10] Of these patients, 58 had clinical convulsions of either the grand mal or psychomotor type, 27 had epileptic equivalents of various kinds, 5 had migraine headaches, 23 had psychiatric manifestations, and 23 had miscellaneous conditions, including, interestingly enough, Huntington's chorea. These authors stated, "The 14 and 6 per second positive spike complex indicates, in our opinion, the presence of an epileptiform disorder which should be treated with anticonvulsant drugs." Kellaway, Moore, and Kagawa reviewed 200 cases of the 14- and 6-per-second positive spike pattern and stated that the pattern itself was not a seizure discharge but a sign of disorder which may have epileptiform manifestations.[18] Additional electroencephalographic abnormalities have been described in the literature.[1,3-5,10,18] It is important that sleep be obtained during the recording of the electroencephalogram, as the 14- and 6-per-second positive spike pattern was noted only during sleep in the great majority of instances.[10] Four brief reports of cases, all of whom manifested this electroencephalographic pattern of 14- and 6-per-second positive spike complexes in sleep records, indicate the varied clinical manifestations of the convulsive equivalent state.

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Report of Cases

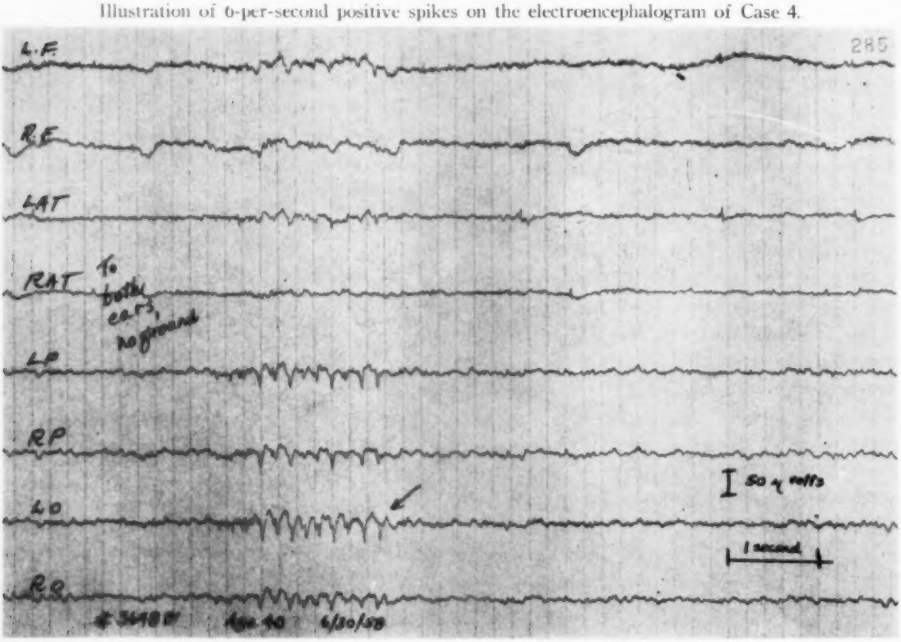
CASE 1.—*Convulsive Equivalent State Associated with Huntington's Chorea.*—This 40-year-old Caucasian woman was first seen with symptoms of extreme nervousness, palpitation, tachycardia, vague abdominal symptoms, headaches, and fits or irritability, rage, and crying. She gave a positive family history for Huntington's chorea, her brother and sister being affected. She related that her symptomatology had been present for about two years. On physical examination, she had a waltzing gait, choreiform movements of the hands and feet, and grimacing of the facial muscles. She exhibited dysarthria, echolalia with perseverence, and emotional lability. Her blood pressure was 160 mm. of mercury systolic and 100 mm. diastolic. The remainder of the physical examina-

tion was negative. Routine laboratory studies were within normal limits. The electroencephalogram revealed paroxysmal 6-per-second positive spikes, nonfocal, and the opinion was rendered that this was compatible with thalamic and hypothalamic epilepsy. The patient was started on therapy with diphenylhydantoin sodium and experienced remarkable relief from her headaches and her gastrointestinal and cardiac symptoms, her blood pressure subsiding to 130 mm. of mercury systolic and 80 mm. diastolic. During a three-month follow-up period, control of these symptoms was maintained. As expected, the symptoms related to her Huntington's chorea, including her mental deterioration, remained unaffected.

CASE 2.—*Convulsive Equivalent State Presenting as a Problem, Paroxysmal Abdominal Pain.*—This 34-year-old Caucasian woman, when first seen, gave a history of paroxysmal abdominal pain of several years' duration. During this period, she had received extensive diagnostic work-ups for gastrointestinal disease. All of these proved negative, and symptomatic medication failed to prevent the paroxysms of abdominal pain. The patient also exhibited marked hostility and emotional lability. The physical examination was unrewarding. In view of the previous extensive diagnostic studies that this patient had received at competent hands, it was felt advisable to consider some of the more unusual causes of abdominal pain. With this in mind, an electroencephalogram was obtained and revealed paroxysmal 6-per-second positive spikes. It was felt that the patient had a convulsive equivalent state. However, the patient was unwilling to undertake a trial on diphenylhydantoin sodium and left the hospital after several bouts of abdominal pain and headache.

CASE 3.—*Convulsive Equivalent State Associated with Psychomotor Epilepsy.*—This 58-year-old Caucasian man was first seen with the history of recurrent severe headaches of about two years' duration and episodes of loss of consciousness, automatic behavior, confusion, palpitation, abdominal pain, nausea, and vomiting. Attacks usually consisted of this entire spectrum of symptoms. His wife volunteered the information that he also had episodes of flushing of the face and pallor associated with some of the headaches. In addition, he had had numerous attacks of pneumonia associated with bronchographically proven bronchiectasis. Physical examination revealed marked corneal scarring due to vesicant gas injuries. Examination of the chest revealed distant breath sounds with occasional moist rales. The heart tones were diminished in intensity, and the blood pressure was 160 mm. of mercury systolic and 110 mm. diastolic. The remainder of the general physical examination and neurological examination was essentially negative. Routine laboratory tests were negative. The electroencephalogram revealed paroxysmal spikes, focal bianterior temporal, indicative of a psychomotor disorder. In addition,

Illustration of 6-per-second positive spikes on the electroencephalogram of Case 4.



there were strong suggestions of a thalamic and hypothalamic convulsive disorder in the form of paroxysmal 6-per-second positive spikes. With the diagnoses of psychomoter epilepsy and convulsive equivalent state, the patient was started on diphenylhydantoin. There was immediate and remarkable improvement in the patient's status, the abdominal and cardiac symptomatology subsiding completely. The blood pressure subsided to 140 mm. of mercury systolic and 90 mm. of mercury diastolic. The frequency of headaches was markedly diminished, and the severity lessened to such a degree that the patient desired to return to his home. The attacks of flushing and pallor of the face and the gastrointestinal manifestations did not recur during a five-month follow-up period with the patient on diphenylhydantoin.

CASE 4.—*Convulsive Equivalent State Associated with Duodenal Ulcer and a Multiplicity of Symptoms.*—This 40-year-old Caucasian man related that he began having "passing out spells" in 1952. These were preceded by a peculiar sensation in the back of the head followed by numbness and loss of consciousness. However, the patient did not have any falls during these episodes except on two occasions. In 1956, he began to have episodes of palpitation, tinnitus, objective vertigo, nausea, vomiting, and indigestion described as "gas in the upper abdomen." Physical examination was essentially negative. Routine laboratory studies were within normal limits. Caloric vestibular tests revealed a normal response in both ears. There was slight perceptive deafness in the left ear. An upper gastrointestinal x-ray series revealed a duodenal ulcer at the tip of the cap. Electrocardiogram revealed sinus bradycardia but was otherwise within normal limits. The electroencephalogram revealed paroxysmal 6-per-second positive spikes, nonfocal, and a diagnosis of thalamic and hypothalamic epilepsy was suggested by the electroencephalographer. The patient was placed on diphenylhydantoin sodium therapy, but he returned home prior to evaluation of his response to this medication.

This patient's electroencephalographic abnormality is illustrated in the Figure.

Treatment

The remarkable improvement exhibited by these patients should be an added incentive to make this diagnosis. Diphenylhydantoin sodium should be tried first, as this medication may be effective by itself in relieving the patient's attacks. The statement has been made that diphenylhydantoin sodium has been so effective that its administration may constitute a therapeutic test.[2] Where diphenylhydantoin sodium alone is insufficient to control the condition, barbiturates, acetazolamide, and trimethadione (Tridione) have been described as being useful.[1,7] Perlstein listed the results with the use of meprobamate in this condition, obtaining no benefit in three patients and aggravation of symptoms in one patient.[16]

Summary

Four case reports are presented as illustrations of the diverse symptomatology of the convulsive equivalent state. In all these patients, electroencephalographic abnormalities in the form of the 14- and 6-per-second positive spike complex were noted, and in two of the patients additional confirmation of the diagnosis was obtained by therapeutic response to diphenylhydantoin sodium. The interesting association of Huntington's chorea with the convulsive equivalent state is reported.

A brief review of some of the literature pertaining to this subject is made, and the necessity for obtaining electroencephalograms during sleep to demonstrate the 14- and 6-per-second positive spike pattern which supports this diagnosis is stressed.

The convulsive equivalent state should be considered when the diagnostician is faced with a patient whose symptoms are paroxysmal and in whom local studies prove negative. The internist should bear in mind that an electroencephalogram interpreted by an experienced electroencephalographer may at times be the key to the diagnosis.

Veterans Administration Center.

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Radiographic Studies of the Lymphatic System

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The radiologic visualization of clinically undetectable lymph nodes and of lymph channels has been successfully accomplished by the injection of contrast media directly into a palpable lymph node. This technique of lymphadenography appears to be a safe and simple method of effecting such visualization.

The procedure was developed during an attempt to evaluate the relative merits of early extensive radiotherapy of localized lymphomas. It seemed desirable to be able to classify more accurately than heretofore those cases which could truly be considered "localized." This is of particular importance when the inguinal and femoral areas are believed to be the only sites involved, since there has been no good method available for delineating enlarged pelvic and lumbar lymph nodes.

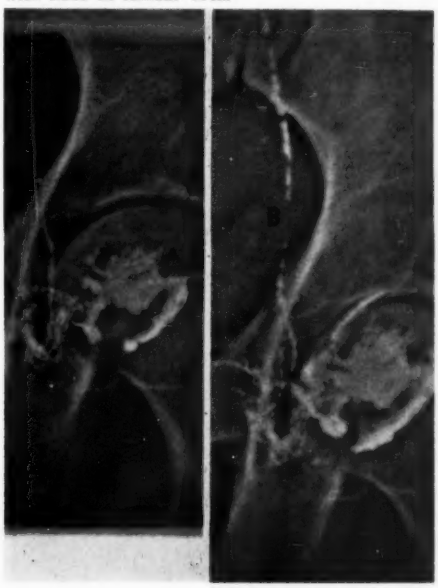
Materials and Methods

In the initial studies several varieties of contrast media were used. Water-soluble preparations were found to be of little value, since they were readily absorbed and did not produce opacification. Colloidal thorium dioxide (Thorotrast) was moderately successful but less so than iodized oil. Iodized oil (Lipiodol) effected satisfactory visualization but, due to its viscosity, was somewhat difficult to administer. Eventually, Ethiodol * (purified iodized ethyl ester of poppyseed oil, each 1 cc. containing 37% by weight of iodine) proved to be the most suitable agent. It was found that the prior injection of hyaluronidase enhanced the ease with which an injection could be carried out and facilitated the spread of the contrast to adjacent lymph nodes.

The skin overlying an accessible lymph node was cleansed with alcohol. With the node held firmly between the thumb and forefinger, 75-150 TRU (turbidity reducing units) of hyaluronidase was injected directly into the center of the node. Once the needle was in place the patient felt little or no discomfort, despite the fact that no premedication or anesthesia was used. The needle was left in place and the syringe replaced by one containing 2-6 cc. of Ethiodol, which was administered at the approximate rate of 1 cc. per five-minute interval. The total amount varied between 2 and 8 cc., depending upon the size of the node, the ease of administration, and spread of the contrast.

During the procedure, repeated fluoroscopic observations were made and spot films taken. Radiographs were taken after completion of the

Fig. 1.—A 49-year-old white man with chronic lymphocytic leukemia. *A*, enlarged lymph node with needle in place. *B*, channel communicating directly with node in lumbar area.



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Present address of Dr. Shanbrom: Orange County Hospital, Orange, Calif. Present address of Dr. Zheutlin: Department of Radiology, U. C. L. A. Medical Center, Los Angeles.

* E. Fougera and Co. supplied the Ethiodol for our studies.

Fig. 2.—Same patient as in Figure 1. Further filling of distant channel with filling of adjacent lymph node.

Fig. 3.—Same patient as in Figure 1. *A*, site of injection. *B*, multiple efferent channels. *C*, lumbar node.

procedure and followed up in one or two hours. A repeat film was made 24 hours later and at monthly intervals subsequently, in order to evaluate results and determine the fate of the contrast material.

Results

Although our technique is similar to that of Brunn and Engeset,[1] we were able, by the previous injection of hyaluronidase, to

Fig. 4.—A 45-year-old white man with Hodgkin's disease. *A*, spot film, showing needle in enlarged cervical lymph node which has been given injection of 2 cc. of contrast medium. *B*, 3 cc. of contrast medium showing channels beginning to fill.

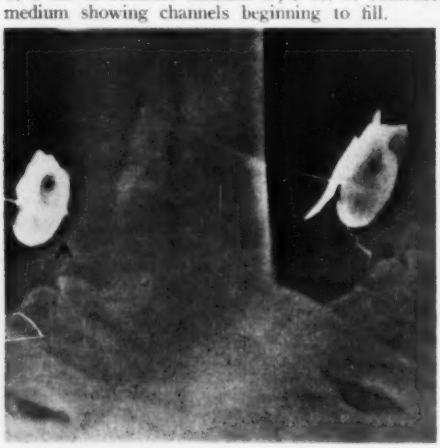
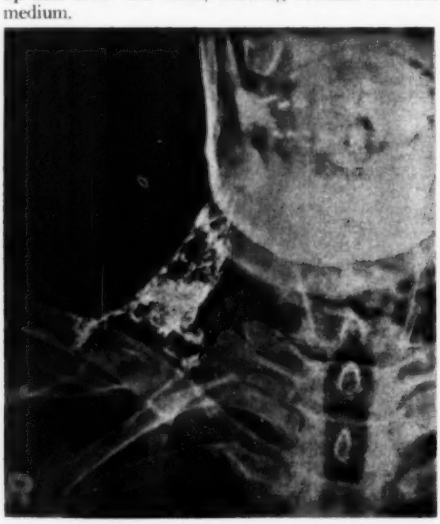


Fig. 5.—Same patient as in Figure 4. Follow-up film after one week, showing residual contrast medium.



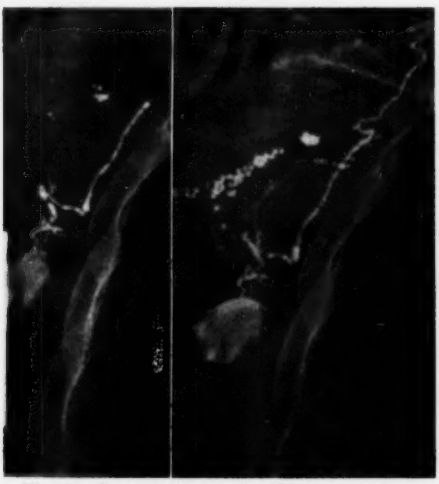


Fig. 6.—Same patient as in Figure 4, with contrast medium injected into enlarged axillary node. The Ethiodol passed from the original site of injection (*A*) along an efferent lymphatic channel (*B*) to the infraclavicular area. Note the droplets of iodized oil appearing in the adjacent axillary vein.

Fig. 7.—Same patient as in Figure 4. Residual oil droplets (*A*) are seen in the vascular channel. Contrast medium traverses the lymphatic channel (*B*) to fill a distal retroclavicular lymph node (*C*).

obtain more frequent successful visualization of enlarged lymph nodes, especially in Hodgkin's disease.

Thirty-five separate injections were carried out in 20 patients with various lymphomas. The patients experienced no discomfort, nor were there any complications in the series. We had anticipated the possibility of fat embolism resulting from the introduction of oily substances into the blood stream. Yet, in spite of the fact that under fluoroscopy we were able to view the passage of iodized oil directly into the

Fig. 8.—Same patient as in Figure 4. Arrow shows additional filling of retroclavicular node. A second axillary node is now more clearly delineated.

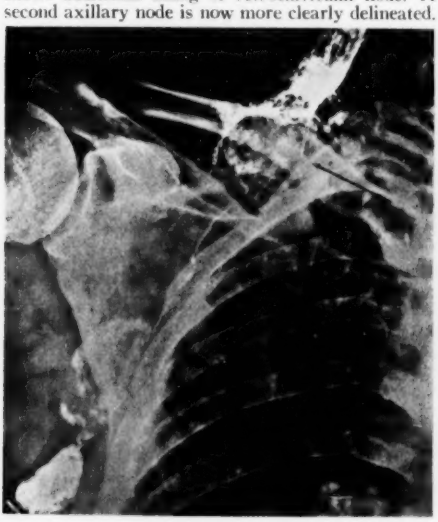


Fig. 9.—Same patient as in Figure 4. Partial clearing of opacified nodes within 24 hours.

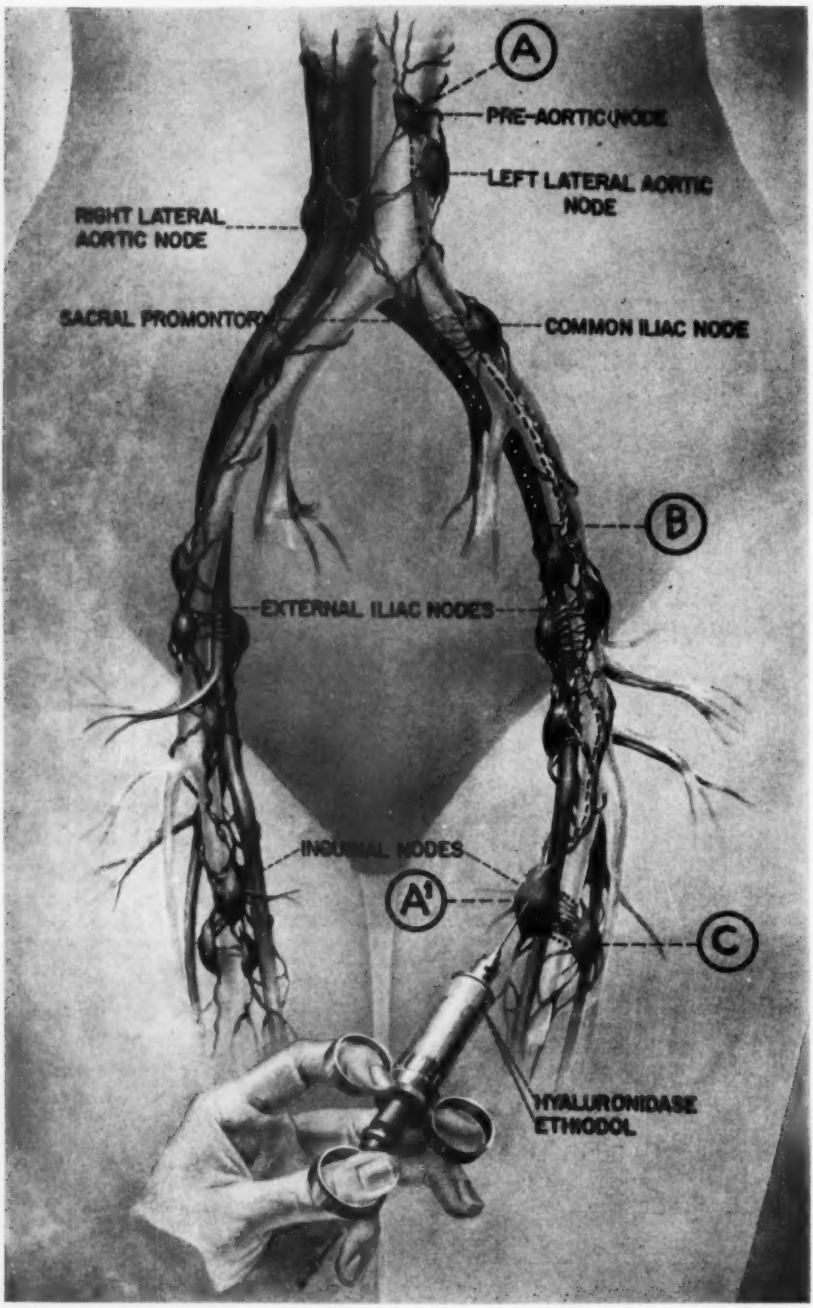


Fig. 10.—Schematic representation of course of contrast medium injected into an inguinal node. After injection of 2-3 cc. of Ethiodol, the enlarged inguinal node is outlined by the contrast medium (*A'*). The material slowly travels along dilated lymphatic vessel, skipping more proximal nodes and filling other distal ones (*A*). Occasionally some of the iodized oil enters the adjacent vein directly from a lymphatic channel and appears in the form of oil droplets (*B*), which then move more rapidly in the blood stream. Lymph nodes most proximal to the site of injection may fill in a delayed fashion (*C*).

blood stream, no such complications occurred (Figs. 6 and 7).

Our study was undertaken initially to detect enlarged pelvic or abdominal lymph nodes. This aim was easily achieved and we were able to visualize para-aortic nodes by injections in the inguinal and femoral areas (Fig. 3). The technique of lymphadenography, however, yielded additional information concerning normal pathways of lymphatic channels. It appears, for example, that there is a direct communication of the axillary nodes with the subclavian vein on that side, as the contrast media could be seen entering the subclavian vessels at several points along its course (Figs. 6 and 7). This may well explain the poor prognosis of breast cancer once the regional nodes are involved. Similarly, injection into the posterior cervical nodes in one case showed multiple lymphatic channels which entered the jugular vein at several points.

Several of our studies have more clearly demonstrated the arrangement of lymphatic channels in general. Of interest is the fact that in one patient with considerable adenopathy in one site, the injection into a single node outlined a major lymphatic vessel before the adjacent nodes became filled with the contrast media (Figs. 1, 2, and 3).

The manner in which the oil traversed the lymph nodes was of interest. Under fluoroscopy, the contrast media could be seen entering the peripheral portion of the node first. With further filling the central portion became opaque and the contrast then advanced to the next group of nodes via the efferent lymphatics. This confirms the findings of other investigators using Direct Sky Blue.[3-5]

Our present technique for visualizing lymph node chains has proved satisfactory, but we are experimenting further in the hope of effecting better visualization of lymphatic channels. Preliminary observations suggest that this may be achieved by the use of aqueous colloidal suspensions of certain contrast agents.

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A Composite of Hereditary Ataxias

A Familial Disorder with Features of Olivopontocerebellar Atrophy, Leber's Optic Atrophy, and Friedreich's Ataxia

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Study of the transmission of neurologic diseases from generation to generation has proved more difficult than that of infectious, vitamin-deficiency, and endocrine disorders. The gains that have been made in the latter fields have no substantial counterpart in the hereditary disorders of the nervous system. Pending further information from geneticists, chemists, and physicists, it is necessary to define and describe the scope of the problem. From the nosologic tangle that has proliferated among the hereditary degenerations of the nervous system, we are presenting observations drawn from the study of a family with a peculiar hereditary disorder having features of three separate entities.

Report of Cases

In May, 1946, a 6-year-old boy who exhibited signs of cerebellar ataxia and optic atrophy was brought to the office of one of us (J. A. W.). His mother said that three other members of the family were similarly afflicted. This led us to study the boy and his family during the next decade.

CASE 1.—The first patient had been apparently well until September, 1945, when he became nervous, emotional, irritable, and uninterested in playing with other children. Previously continent, he now wet his bed at night. These signs increased, and he began to tire easily. One day his brother was surprised because the patient was unable to see objects in a store window. By midafternoon he would lie down and sleep as though exhausted, and he seemed uncertain on his feet when he walked, occasionally staggering and complaining of headaches but not of dizziness. By the time he came to medical attention, he could not walk upstairs erect and used banisters for guidance and support. Although his appetite remained good, eating became difficult because of spilled food, jerky movements, and wide pendulating tremors.

This patient was the last-born of five children, all boys, delivered at full term after normal pregnancies. A photograph taken at seven months (Fig. 8) shows him apparently normal and alert. He was standing at 9 months, was walking and talking by 13 months, and began school at 6 years, but his illness had so progressed that he left school after two months.

The boy was well developed and rather thin, with the uncertain, distrustful frown of the partly blind. He was cooperative, although querulous. Height and weight were normal. The head appeared narrow and long, and there was a rounded prominence approximately 6.5 cm. in diameter in the midfrontal region. Examination of the eyes showed normal extraocular movements, clear conjunctivae and corneae, and strongly dilated pupils which reacted slowly to light, individually and consensually. The ophthalmoscope revealed clear media but unusual fundi. The optic disks were large and the temporal halves severely pale, but the areas of the macula lutea were normal. The retinae were pale, with few blood vessels, and degenerated in spotty areas but without hemorrhages or exudates. Visual acuity was less than 20/200 in each eye. The tonsils were hypertrophied and deeply cryptic, but the nose and pharynx were otherwise normal. The neck, chest, lungs, heart, and abdomen did not provide notable findings on examination, and the genitalia were normal. The

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extremities showed full range of active and passive motion, with slight general loss of strength.

The patient was restless and spoke with a nasal or "bulbar" intonation. Swallowing liquid readily caused choking, and occasionally fluids ran back from his nose. The deep and superficial reflexes were normally active and equal on the two sides. Abnormal reflexes could not be elicited, and the Romberg test was negative. Coordination, however, was markedly impaired. The gait was slightly ataxic. Movements were jerky, almost explosive, with overcorrecting antagonistic movements, and adiadochokinesis was present. Ataxia interfered with finger-to-nose, finger-to-finger, heel-to-knee, and toe-to-finger tests. Pain, touch, vibratory sense, and stereognostic perception were normal within the limits of his cooperation. Routine blood cell count, analysis of urine, and a serologic test for syphilis (Mazzini flocculation) yielded normal or negative results.

The course was marked by relentless deterioration until death, in September, 1949, four years after onset, and is conveyed in the following summary, copied from office notes:

June, 1946—tonsillectomy. Exhibited weakness and staggering; occasional rhythmic tremors, especially when nervous or tired; pupils more widely dilated; increasing retinal cystic and pigmentary degeneration.

January, 1947—measles.

April, 1947—further ataxia and weight loss; gait jerky with high slapping steps as if going upstairs; biceps and triceps reflexes hyperactive on left; knee jerks hyperactive and equal; clonus and Babinski sign absent.

September, 1947—unable to see large objects; can only distinguish light from dark; crawls but cannot walk or feed self; cries often as though frightened; marked emaciation; lies with lids half open, occasionally tries to open eyes with a leering expression of the mouth and asymmetrical lifting of the forehead and eyebrows, right side of face drooping; talks infrequently and with increased bulbar quality of voice; petulant and disagreeable at slight provocation; smiles when tickled, able to count to 20, sings with radio music and recites nursery rhymes; increasing retinal degeneration.

July, 1948—pain in right leg for two weeks; roentgenogram reveals unsuspected fracture of upper third of tibia; history then obtained that father (also ataxic) had attempted to pick the patient from the floor and the boy's leg had caught under a chair; cast applied and fracture healed with good functional recovery.

November, 1948—head drops forward while sitting, chokes while eating and sometimes gets cyanotic; can stand on legs when forced but cannot walk; vomits occasionally; using Adirondack chair.

February, 1949—acute keratitis on left due to incomplete closure of lids.

May, 1949—left corneal scar; eats strained foods only; chokes on solids; weight 31 lb.; says a few syllables intelligible only to his mother.

July, 1949—unable to swallow food; taking only sips of eggnog and other fluid; constant choreiform movements, grimaces occasionally; pulse 130; utters only animal cries for speech.

Sept. 1, 1949—died after developing signs and symptoms of pneumonia.

Necropsy was performed about three hours after death on an emaciated white boy whose body exhibited complete absence of subcutaneous fat and severe atrophy with rigor of the muscles of the extremities. Livor was absent and all tissues were dry and pale.

Examination of the organs revealed normal structures except for intense bilateral focal pneumonia with early abscess formation and irregularities in size and staining qualities of voluntary muscle fibers, without diagnostic alterations.

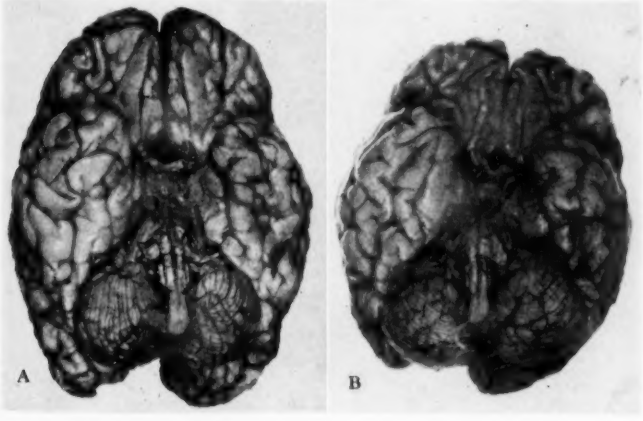

Fig. 1.—Ventral surface of brains of Cases 1(*A*) and 2(*B*). Decrease in size of pons and cerebellum and enlarged basal cisterns are seen in both specimens.

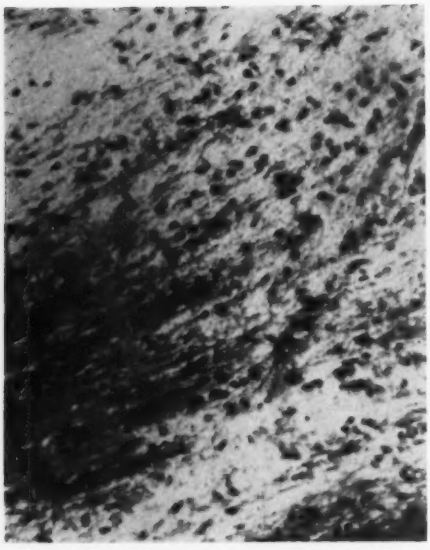

Fig. 2 (Case 1).—Optic chiasm. Margin of zone of extensive demyelination with ragged ends of myelin sheaths. Myelin sheath stain; × 100.

The brain weighed 1,060 gm. The convexities were normal, but inspection of the ventral aspect showed atrophy of the cerebellum, olivary nuclei, and pons (Fig. 1*A*). Macroscopically, the spinal cord was not atrophic or softened and the fiber tracts appeared normal. The optic tracts were hard and white; the lateral geniculate bodies were atrophic; the transverse pontine fibers were decreased in size and number.

Microscopic examination of the visual system revealed a striking decrease in the number of cells in the ganglion layers of the retina and blurring of the outer margin of the fiber layer. Severe demyelination was seen in the optic chiasm, with large amounts of neutral fat in phagocytes (Fig. 2). Nerve cells were altered or lost, and small areas of softening were noted within the lateral geniculate bodies (Fig. 3). Minor changes in the cerebral cortex consisted of loss of ganglion cells in the vicinity of cerebral arterioles that were thick-walled for a 10-year-old boy. These changes were noted in the occipital lobes, but elsewhere, the cortical cellular architecture in Nissl-celloidin sections was within normal limits. Some ballooning of myelin sheaths was observed in appropriate stains of the cerebrum. The appearance was of a secondary alteration and not a primary demyelination. There was a minor loss of ganglion cells in the globus pallidus; the caudate, putamen, thalamus, and mammillary bodies were cytologically normal in appearance. The cerebellum had undergone striking alterations, chiefly affecting the Purkinje- and granular-cell layers. The molecular layer and white matter were moderately gliotic. Nearly all the Purkinje cells had disappeared, and the survivors were scattered, usually singly, along the edge of the granular layer, which was composed only of ghost-like cell remnants and glia (Fig. 4).

Stains of the myelin sheaths in the cerebellar folia showed extensive loss and alteration. Large numbers of sheaths were, nevertheless, still present, and the appearance again was of a more striking degree of degeneration than that observed in the cerebrum but nevertheless a secondary one. The pontine nuclei were less cellular than usual. The remaining cells were normal, except that occasional bizarre and irregular nuclei were seen or the nuclei were displaced to the edge

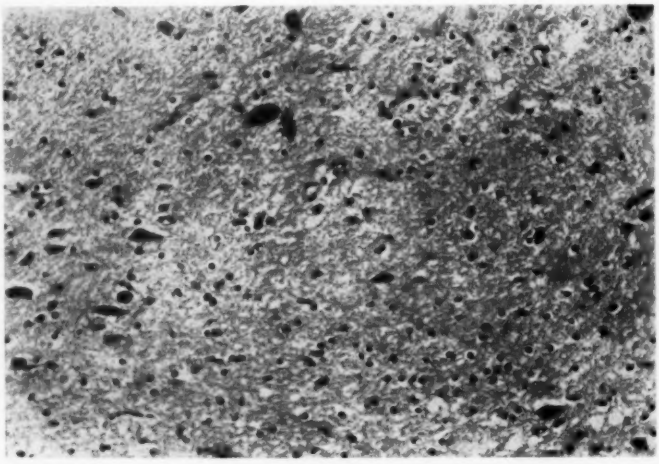

Fig. 3 (Case 1).—Lateral geniculate body. Loss of laminar structure, as well as shrinkage of ganglion cells, with decrease in number of these structures, and loss of intercellular substance. Hematoxylin and eosin; × 100.

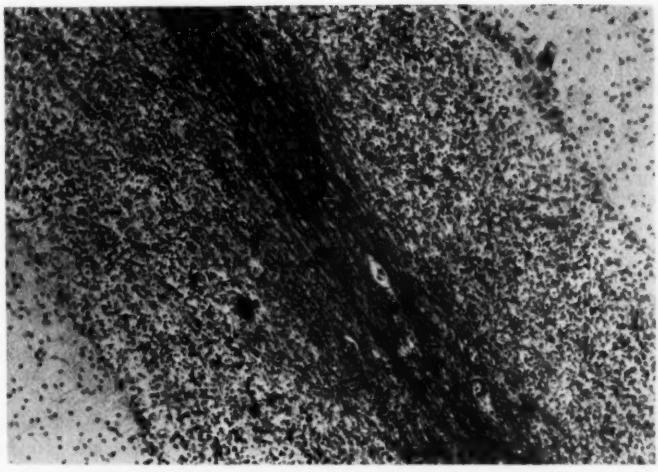

Fig. 4 (Case 1).—Cerebellum. Absence of Purkinje cells, marked decrease in granular layer and gliosis of molecular layer. Hematoxylin and eosin; × 100.

of the cytoplasm. The cells of the inferior olivary nuclei were absent and replaced by glia. Neurons of the cranial nerve nuclei were slightly shrunken.

The spinal cord was severely demyelinated in the posterior columns and irregularly demyelinated in the lateral columns, chiefly in the spinocerebellar tracts (Fig. 5). Sudan stains for fat confirmed these findings. Maximal quantities of neutral fat were seen in the posterior columns. In the lateral columns, neutral fat was seen only in phagocytes around blood vessels, indicating that the changes in these columns were of greater duration. There was a significant loss of anterior horn cells at the lumbar level, but the nerve cells were normal at other sites.

The final diagnoses were as follows:

1. Degenerative neuronal and myelin sheath changes of the central nervous system, comprising
   (*a*) Retinal degeneration with atrophy of optic tracts and lateral geniculate bodies
   (*b*) Olivopontocerebellar atrophy
   (*c*) Posterolateral column degeneration of spinal cord
2. (*a*) Generalized wasting with muscle atrophy
   (*b*) Bilateral focal pneumonia

Comment.—The findings are those of olivopontocerebellar atrophy but with additional features. These include widespread degeneration of the optic pathways and lesions in the spinal cord resembling Fried-

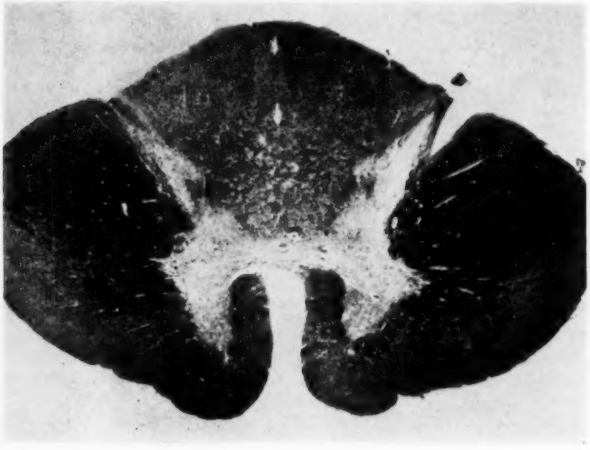

Fig. 5 (Case 1). — Spinal cord, midcervical region. Illustration shows marked demyelination of the posterior columns and, to less degree, of the spinocerebellar tracts. Myelin sheath stain; × 10.

reich's ataxia. The changes in the cerebrum are nonspecific and appear in many "degenerative" disorders.

Case 2.—The father of Case 1 had been well and working in an insurance office until 1935, when decrease of visual acuity interfered with his work and he was retired with partial disability, at age 34. He was weakened by an attack of lobar pneumonia later that year and thereafter experienced further loss of vision, of weight, and of sense of equilibrium. The records of another hospital show that in 1936 the vision of his right eye was 20/70-20/100 and of the left eye 20/100-20/200, with bilateral central scotoma. He began to use a cane in 1941, but despite staggering, lack of coordination, and failing vision he continued to drive his car until 1943.

He was first seen by one of us (J.A.W.) in 1946, complaining of blindness, staggering gait, and choking on food as though "unable to control the swallowing muscles." There was no vertigo, but since 1936 he had frequent headaches attributed by him to eyestrain. He had lost about 25 lb. since onset, but this process had halted five years previously. The patient had completed high school and college; he had suffered pneumonia, pleurisy, and influenza and had undergone operations for removal of tonsils, adenoid, and prepuce.

He was a tall, lean, well-developed man with normal vital signs. He walked with the aid of a cane but bent markedly forward at the hips to see the ground and to avoid falling backward. The base of his gait was wide, and he raised his feet high, slapping the floor with jerky movements. The arms jerked as he walked. His skin was pigmented over the legs, and the head was long and narrow, with an 8 cm. round midfrontal boss. The ears were normal, as were the eye movements. Pupils and reactions were normal save a sluggish response to light. The temporal halves of both optic disks were pale. The nerve heads were surrounded by narrow bands of black pigment. Other than carious teeth, the extraneural organ systems were normal. There was widespread loss of body fat and general muscular atrophy, but muscle strength was nearly normal. Sensorium and memory were clear; he was cooperative and of average intelligence. The skin and tendon reflexes were hyperactive and equal; there was ankle clonus, severer on the right, but no other pathologic reflexes. Speech was nasal or bulbar in quality. Coordination was poor, and adiadochokinesis was striking. Ataxia and explosive, jerky movements attended finger-to-nose, finger-to-finger, and heel-to-knee tests. Abnormalities of sensation were not demonstrated.

Laboratory examinations, including a routine blood cell count, Mazzini flocculation test, analysis of urine, and roentgenogram of the skull, yielded negative or normal results. An electrocardiogram indicated normal sinus rhythm and left axis shift with no abnormalities.

This patient deteriorated steadily. In June, 1947, he was committed to a state hospital because of delusions of marital infidelity, threat of bodily harm to his wife, and evidence of deterioration of intellectual and emotional affect. At that time he was found to have intention tremor, absent superficial reflexes, and increased deep reflexes. Cerebrospinal fluid examination showed a negative Wassermann test and a gold curve of 1112221111. Roentgenograms of the chest and skull were normal. Psychiatric examination showed a flat affect and amnesia for the psychotic events leading to admission. He was well oriented in all spheres, had a prominent memory impairment for recent and remote events, and had no knowledge or interest in current events. Judgment and insight were defective. He was discharged from the hospital after the legal commitment period of 30 days and made a satisfactory adjustment to invalid life except for emotional instability, as shown by flare-ups of temper over trivia.

All his teeth were removed in October, 1951, because of apical abscesses. He was reexamined because he was losing weight, was occasionally confused, and complained of aching legs. He was confined to bed at this time. There was severe incoordination in the tests of cerebellar function in both hands and legs, with marked rebound phenomena. Motor power was moderately good in spite of severe atrophy. There was some flexion contracture of the knee joints. All deep reflexes were abnormally hyperactive; there was striking bilateral clonus, but the Babinski response was flexor in type on one occasion, and there was no response on other trials.

Vision had decreased to the level of light perception and recognition of fingers at a short distance. Both optic disks were atrophic and pale white, but the cups were full, suggesting underlying gliosis. Pupils reacted poorly to light but moderately well in convergence. Upward movements of the eyes were limited, but eye movements were otherwise normal. The other cranial nerves were intact except that the tongue was moderately incoordinated when protruded. Sensory examination revealed absence of position sense in hands and feet. Touch sensation and stereognosis were intact. Speech was incoordinated. The patient was generally cooperative and voluble.

By January, 1953, he could perceive light dimly. The previous findings were still present, and twitchings were noted in the deltoid muscles. Touch and pain sensations were intact. Tendon reflexes were hyperactive; clonus persisted, and the Babinski sign was absent.

The signs were further accentuated early in 1955. The man spent his day in a chair. Any change of position caused explosions of spontaneous clonus. All movement was weaving and pendular in type, with overshooting and overcorrecting, jerky incoordination, dysmetria, and asynergia. He was incapable of skilled acts. The speech was nasal and bulbar in quality, with hoarse crowing inspiratory noises and a thick, slow, incoordinated tongue. There were frequent myoclonic twitchings in small muscle groups. Facial grimacing accompanied efforts at speech. He had fits of petulant anger and occasionally of profane abuse of his wife. During late winter and spring of 1957 mobility decreased and the general condition was progressively impaired until on April 11, when the patient died with signs and symptoms of pulmonary infection.

Necropsy was performed 12 hours after death. The body was extraordinarily wasted, especially in the muscles, and there were large decubiti. The right lung weighed 1,100 gm. and was the site of extensive confluent pneumonia. The right lower lobe contained an abscess 5 cm. in diameter, from which heavy growth of coliform bacilli and nonhemolytic streptococci were obtained. Stains of the pus for acid-fast bacilli were negative. The other organs were of normal appearance and were slightly less heavy than normal.

The spinal cord and its meninges were unremarkable in appearance. The brain weighed 1,200 gm. The cerebral hemispheres were symmetrically atrophic, with corresponding enlargement of the sulci and cisterns. This increase in size of the subarachnoid reservoirs was especially noticeable about the hindbrain, as a result of severe atrophy of the pons and medulla (Fig. 1*B*). The optic nerves were atrophied, but the cerebellum was not. Serial coronal sections of the brain revealed pallor of the basal ganglia and striking decrease in size of the optic tracts and of the lateral geniculate bodies. The gray and the white matter of the pons and the white matter of the cerebellar peduncles were greatly decreased in bulk. The dentate and inferior olivary nuclei were small, and the cerebellar nuclei were discolored a light brown-gray. The other cerebral structures were free of gross changes.

The microscopic features of this case corresponded with those of Case 1 in general, but there were some differences in presence or degree of alterations. The retina was even more severely atrophic than was seen in the son (Case 1), with complete disappearance of ganglion cells and only partial survival of the outer nuclear layer and faint shadows of the rods (Fig. 6). The optic nerves, chiasm, and tracts were extensively demyelinated. The lateral geniculate bodies were shrunken, with hyperpigmentation of the ganglion cells and disorganization of the laminar structure. In addition, severe loss of substance around the geniculate cells was noted and attributed to extensive atrophy and demyelination of the fibers of

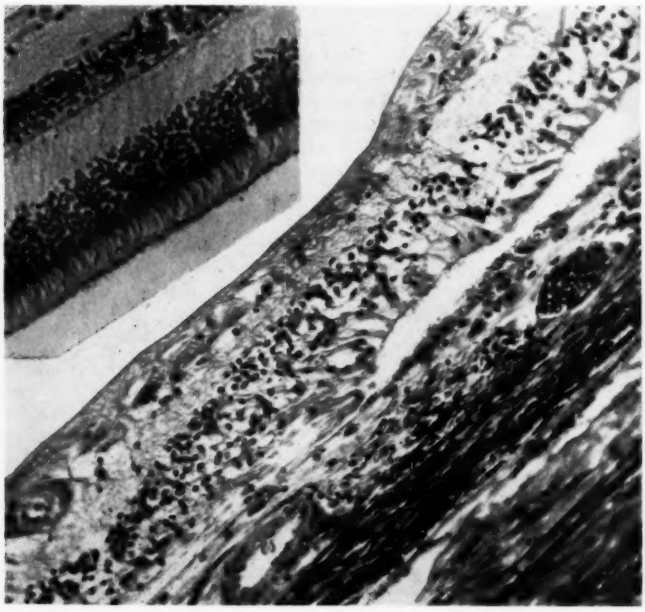

Fig. 6 (Case 2).—Retina. Extensive ganglion-cell and fiber layer damage, with loss of substance and almost complete loss of cells. Shows normal retina, similarly oriented and photographed at the same magnification. Hematoxylin and eosin; × 430.

the optic tracts as they arrived within the geniculate bodies.

Survey of the frontal, temporal, parietal, and occipital cortex revealed a moderate degree of shrinkage of ganglion cells, pyknosis of nuclei, and loss of Nissl substance. While the conventional interpretation of such findings are that they represent a variable degree of premortem cell damage and attributable to hypoxia or other less specific forms of injury, we are at present not confident that this is so. The recent work of Lindenberg[1] indicates that the degree of hypoxia during the period of time just before death and the temperature at which the brain is kept before fixation may themselves produce or suppress cell changes of this type. We therefore believe that the cortical ganglion-cell changes in this case should not be attributed to the basic disease process or its complications.

In the hindbrain the cerebellum was the site of extensive loss of Purkinje cells. There was a striking difference from the cerebellum in Case 1; the granular layer was intact, but in the former instance it had virtually disappeared. In the dentate and inferior olivary nuclei, the ganglion cells had largely disappeared. The few surviving cells were atrophic and hyperpigmented, with gliosis of the remaining structures.

The spinal cord at all levels had a marked decrease in the number of fibers in the regions of the dorsal and ventral spinocerebellar tracts. These changes were far less prominent in the posterior columns, but in both areas small amounts of neutral fat were seen in macrophages in the tissues and around blood vessels. In the lower thoracic and lumbar cord there was a suggestion of decrease in number of anterior horn cells. Some distinctly normal-appearing ganglion cells were present at all levels.

The final diagnoses were

1. Degenerative and myelin sheath changes of the central nervous system comprising
   (*a*) Retinal degeneration with atrophy of optic tracts and lateral geniculate bodies
   (*b*) Olivopontocerebellar atrophy
   (*c*) Posterolateral column degeneration of spinal cord
2. (*a*) Generalized wasting with muscle atrophy
   (*b*) Confluent focal pneumonia, right lung, with abscess formation, right lower lobe

Case 3.—A boy, son of Case 2 and elder brother of Case 1, had a normal birth (1926) and childhood. His mother first noticed that he was losing vision when he was 14 years old, and then his gait became progressively unsteady. Despite this he graduated from high school with average grades and worked as a packer. He was first seen by us in 1946, complaining of locking of his right knee for a year. Review of systems disclosed only some dyspnea of exertion. He was a tall, muscular, healthy-looking young man, intelligent and cooperative. Vital signs were within normal limits, save an initial blood pressure reading of 162/80. The findings on general physical examination were normal. The extraocular movements were sluggish and incoordinated, and the pupils were markedly dilated but reacted to light and in convergence. Ophthalmoscopic examination showed patchy pigmentation of the retinae and pallor of the optic disks bilaterally. The sensory modalities functioned normally, but the patient had an ataxic gait, hyperactive deep tendon reflexes, bilateral abortive ankle clonus, slurring of speech, and athetoid movements.

There was a progressive loss of vision and increasing ataxia, and so within a few months he was forced to give up his job because of permanent and total disability, eight years after the onset. His symptoms were causing great emotional stress. He tired by early afternoon and found it difficult to form words, to place his feet accurately, and to handle small objects. He was often hungry and drank large amounts of water; he perspired easily but did not have urinary tract symptoms. Reexamination confirmed the previously recorded vital and neurologic signs, and the light reflex had disappeared. Visual acuity was less than 20/200, and near vision was extremely blurred. Sensory perception was otherwise intact. The Romberg test was negative. Muscle strength was still good, but coordination was impaired and an intermittent coarse tremor of the hands had appeared. The gait was broad-based and incoordinated, with the heel thudding forcibly and staggering to either side on turning. The voice had a nasal or cleft palate quality with a slightly explosive "f" and incoordination of phonation.

A lumbar puncture was done at the home of the patient in 1949. The cerebrospinal fluid was clear; pressure and dynamics were normal. Total protein concentration was 48 mg. per 100 ml., a complement-fixation test for syphilis was negative, and a colloidal gold curve was 5552200000.

An electrocardiogram in 1950 showed sinus tachycardia and was interpreted as suggesting myocardial damage. The P-R interval was 0.16 second, QRS was 0.10 second, and QRST was 0.28 second, with small Q_3 and depressed ST_3 and ST_2.

In 1951 he could take only a few steps on a wide base, if supported. The steps were small and jerky. There was generalized incoordination and inability to perform rapidly alternating movements. Occasional pseudoathetotic movements were seen. Motor power was remarkably good. Sensory examination revealed mild loss of position sense and hypesthesia over the hands. Examination of the cranial nerves demonstrated almost complete blindness. The optic disks were swollen one diopter and

did not have sharp edges; the appearance was of residual rather than active papillitis. The pupils were widely dilated, with some reaction to convergence but not to light. Speech was explosive and incoordinated. The other cranial nerves were intact. The deep reflexes were again notably hyperactive. Clonus in the lower extremities was so striking that it resembled "spinal epilepsy." Despite this the sign of Babinski was not definitely present although on this occasion flexor responses were never obtained.

In August, 1953, a trapezoidal area of cystic degeneration was found lateral to the left optic disk. In November, he fell while trying to walk out to the kitchen, injuring his left shoulder. At the present time he is bed-ridden, is emaciated, chokes on food, has nightmares that cause him to cry out in fear, and has withdrawn into deep despondency.

CASE 4.—The second of the children was born in 1929 and was entirely well until the age of 15. His eyes were tested annually at school, and visual acuity had always been 20/20. Then, in 1944, it had decreased to 20/50 and later to 20/100. Meanwhile he began to notice that when tired he would be unsteady on his legs, staggering occasionally.

Initial examination in 1946 showed a well-developed, friendly, well-nourished and oriented youth whose vital signs were normal and who did not appear ill. The general physical examination revealed only an increased second pulmonic sound and an accentuated aortic first sound. The cranial nerves yielded significant data in the ocular system only. Ocular movements were normal; ophthalmoscopic examination showed clear media, moderate pallor of the optic disks, and normal retinae and retinal vessels. There was a peculiar slow blink, and the moderately dilated pupils reacted readily to light and convergence. There was no nystagmus. The gait was unsteady, with a heel thud. Deep and superficial reflexes were active to slightly hyperactive but symmetrical. Abnormal reflexes were not found. His speech was slurred and slow because of poor coordination of tongue and mouth movements. All bodily movements were slightly incoordinated. Muscle power was intact, as were the sensory modalities.

Blood cell count, analysis of urine, and a Mazzini serum flocculation gave negative results or normal values. The cerebrospinal fluid had a total protein concentration of 52 mg. per 100 ml.; complement-fixation test for syphilis was negative, and a colloidal gold curve was 3355320000. An electrocardiogram in April, 1950, was normal.

This boy, and his brother (Case 3) had suffered relentless progression of blindness and ataxia. Case 4 was forced to give up a factory job in 1947 and simpler farm work in 1949. Since then his bed-to-chair existence has been lightened only by radio and phonograph records. Both optic disks are flat and atrophic, and he complains of swallowing difficulties with occasional nasal regurgitation of fluids.

Family History

There are two other children in the family, Case 5, born in 1931, and Case 6, born in 1933. Repeated examinations of these boys have been made since 1946, and to date no evidence of disease had been found in either. Both have enlisted in the Navy, both had overseas duty and have been honorably discharged without disability. Case 5 was married in 1953. His wife has had one spontaneous abortion and has since had a normal boy. Case 6 married in 1956 and has a normal son, born in 1957.

The family tree is depicted in Figure 7. It will be seen that the only antecedent providing a suggestion of the origin of the illness in the present generations is the children's paternal great uncle, who was

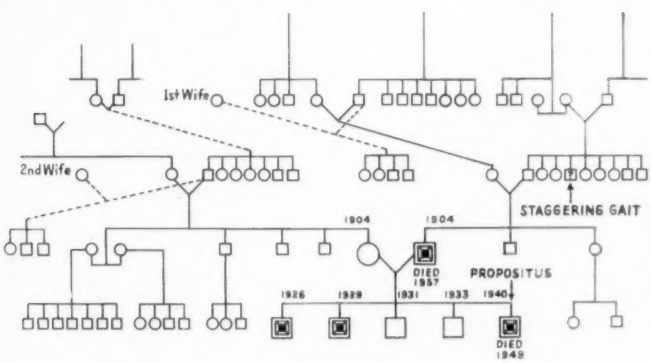

Fig. 7. — Genealogic chart of the family, indicating apparent abrupt appearance in present generation, with only suggestion of involvement in great uncle of propositus.

Fig. 8 (Case 1).—First three pictures taken while well. Lower right photograph taken during early stages of blindness and ataxia.

said to have had a staggering gait. The mother and the wife of Case 2 are the only other members of the family whom we have seen personally. A collection of photographs of Case 1 shows clearly, especially in the last frame, the changes in physical appearance and facial expression accompanying the development of the disease (Fig. 8).

Methods of study of a familial-hereditary disease are well outlined in monographs by Refsum [2] and Lundsgaard.[3] B. Sachs is quoted by Refsum as follows: "In describing a new form of disease it is desirable that all possible symptoms should be clearly set forth. . . ." According to Refsum, an investigation of heredity based purely on questioning is practically worthless, ". . . for by such procedure misleading information is so often obtained, partly because the informants do not know enough about the persons concerned, and partly because they may deliberately withhold information. Lastly, without a complete examination of the whole family we are bound to miss the rudimentary forms of the disease wherein diagnosis can only be made by an expert physician." Lundsgaard's monograph [3] on Leber's optic atrophy is a classic

example of such a study properly conducted.

By such standards this presentation cannot qualify as a thorough genealogical study of this family. The family tree is exhibited as a part of the description of a degenerative disorder that has appeared in four men and two generations of a family. It attracted our attention because the disorder reproduced itself in each case as a syndrome incorporating the features of three other syndromes, Leber's optic atrophy, olivopontocerebellar atrophy, and Friedreich's ataxia.

Comment

Social and scientific observations of Homo sapiens (var. medicus) have shown that he tends to function as a "splitter" or as a "lumper." The "splitter" is most active during times when certain diseases are poorly understood and imperfectly treated; under these circumstances classification, subclassifications, and sub-subclassifications appear. The "lumper" usually belongs to the days when complicated categories of maladies give over to unification of multiple syndromes and variants, as competent causes and effective remedies make their appearance. Some persons function as "lumpers" or "splitters" as a trait of character or personality, rather than from the influence of the contemporary medical scene. In either case, until recently the heredofamilal degenerations of the nervous system have been a happy ground for "splitters," and it is with some satisfaction that we record "lumper" activity in this field and offer some data from this family.

Lambie et al.[4] and Gray and Oliver[5] have reviewed the work of Friedreich, Dejerine and Thomas, and Pierre Marie and have suggested that much dispute over the exact boundaries separating spinal ataxias from cerebellar ataxias has failed to establish each as a sharp entity because the clinical as well as the anatomic features of each tend to merge and overlap. This movement toward amalgamation contrasts with that taken by two contributors,[6,7] who subdivide "primary" ataxia, Dejerine-Thomas or olivopontocerebellar (hereditary) atrophy, Foix-Alajouanine ataxia (cortico-cerebellar atrophy), and multiple sclerosis. A contribution by Hassin[8] emphasized two notions of interest to "lumpers." The first was that the cerebellar and spinal ataxias produce more marked and outspoken anatomic alteration when they develop as familial disorders than as single sporadic cases. His second observation was that the clinical features of the cerebellar and spinal ataxias may overlap with each other, as well as with those of multiple sclerosis and the amyotrophic lateral sclerosis group.

The interweaving of patterns in some heredodegenerative diseases is illustrated in a paper by Ross,[9] who described two brothers with illnesses combining Friedreich's ataxia and Charcot-Marie-Tooth atrophy. A sister had Friedreich's ataxia, and a cousin had spastic paraplegia. Ross postulated that some families are subject to a common genetic vulnerability of certain tracts of the nervous system, the degeneration of which may occur in simple or complex fashion and produce mild or complicated neurologic disturbances.

An important contribution by Sjögren[10] exploited the statistical approach ("lumping") and demonstrated interviewing on a grand scale by studies of 188 cases of heredoataxia in 118 families. Eighty-four cases had reasonably typical cerebellar ataxia, and sixty-four were typical Marie's ataxia. Two other groups of patients, numbering 17 and 12, respectively, were designated as resembling one major group more than the other. A fifth and small group, of 11 cases, was designated as "fragmentary." Sjögren has provided two other pertinent observations: first, that progressive dementia is common in both of these major forms of ataxia, and second, that the average age of onset for Friedreich's ataxia was 13 years, for Pierre Marie's disease 34, and

for the heterogenous groups about 50. He noted that in any particular family and particularly within a group of siblings the age when symptoms began was often the same. Nevertheless, Sjögren maintained there was an essential difference between Friedreich's and Marie's ataxias, because the former behaved as a genetic recessive and the latter as a genetic dominant. He expressed the opinion that the two major diseases represent two fundamentally different biotypes, although his data can be interpreted as the expression of multiple alleles.

Another impressive large scale study, by Schut,[11] included 342 persons in six generations of a family. Of these descendants of a common ancestor, 45 had ataxia and could be classified according to major symptom complexes into three groups: (1) hereditary spinal ataxia, (2) hereditary cerebellar ataxia, and (3) hereditary spastic paraplegia. In this family, ataxia appeared as a dominant trait. Optic atrophy was found in four members—most of them with a Friedreich's type of ataxia—a much lower incidence than that reported by Sjögren. Neurologic changes indicating cranial nerve damage, as well as cerebellar, general sensory, motor, muscular, and autonomic nervous system damage or imbalance, were common. Schut summarized features emphasized by Londe (Marie's pupil) for the distinguishing of Friedreich's and Marie's ataxias, but it appears that he encountered difficulties in applying them.

François and Descamps[12] and Franceschetti and Klein[13] reported families and a single patient (respectively) in which the presence of retinal pigmentation enters the clinical picture of both familial and sporadic ataxia. One of the papers added a wide band of mental, auditory, somatic, and endocrine disturbances, properly viewed as variants on a major theme rather than a series of independent compositions.

The ocular features are of interest in the family described in this paper. Although the ages of onset were 5, 34, 14, and 15 years, respectively, symptoms of failing vision were the initial complaints of all four. In two of them the illness was diagnosed Leber's optic atrophy, and it was necessary to examine the evidence for this carefully before widening and lumping the diagnosis. The features of this disease as set forth by Leber and by Lundsgaard[3] are that it is hereditary, non-sex-linked amaurosis caused by neuritis or neuroretinitis. The onset is described as sudden bilateral loss of visual acuity due to central scotoma, with blurred and discolored disks. The peripheral fields are often normal, and color blindness sets in over the entire field. It is observed that the prognosis for vision is not always bad. Lundsgaard describes *another* disease resembling Leber's but differing in being of dominant genetic character and with minor clinical differences. Still another form of optic atrophy with hereditary features, spinal cord signs, and ataxia has been described[14] and labeled the syndrome of Behr. Van Bogaert[15] has written concerning the linkage of optic and cerebellar atrophy and suggests that sclerosis of the ophthalmic artery should be considered in the production of optic nerve changes.

In reviewing a group of papers[16-18] of chiefly clinical character, we found one[18] with a case report describing a patient similar to our Case 1. Optic atrophy and cerebellar signs, ascending degeneration of the spinal cord, and onset at age 9 were described. Myocarditis,[19] which may occur in Friedreich's ataxia, has not been found in our cases either at autopsy, clinically, or by electrocardiographic study. We have not encountered myocarditis in any reports of olivopontocerebellar atrophy.

The case of Lambie, Latham, and McDonald,[4] called olivopontocerebellar atrophy, may be compared with our patients. They described a 59-year-old man who died after a three-year illness beginning with hemiplegia and diplopia, followed by masked face, tremors, cogwheel rigidity, festination, and retropulsion. These symp-

toms increased and there were rigidity, emotionalism, exaggerated knee jerks, and loss of bladder control. In contrast to the severe rigidity described by Marie and Dejerine-Thomas and illustrated by Lambie et al., our four patients had spasmodic muscular contractions and exaggerated muscular movements. Other differences are those between the histologically normal eyes described by Lambie and the striking alterations in the eyes of our autopsied patients, and between the changes he found in the basal ganglia as compared with the minimal and probably secondary changes found by us in the pallidum. Also, whereas our autopsied cases showed major changes in the cerebellum, pontine nuclei, posterior columns and spinocerebellar tracts, Lambie's case featured myelin loss in the ventral spinocerebellar tracts, the transverse pontine nuclei, the basal ganglia, and Purkinje cells. A more clearly contrasting feature of his case was the more distinct sparing of the cells of the granular layer of the cerebellum.

Greenfield's monograph [20] on the spinocerebellar degenerations deals with classification at three levels. The first simply names three groups: spinal, cerebellar, and spinocerebellar. The second is an examination of cerebellar ataxia alone and designates four congenital and four acquired types. The third is an elaboration of the first and gives some attention to peripheral neural and neuromuscular disorders. This publication provides a full discussion of the larger family studies, the results of clinical observations and correlations, and the relation of visual or mental changes to the spinocerebellar disorders.

Cobb and Bereday [21] have codified and consolidated the essential unity of a wide group of familial neurologic disorders and indicated their relation to diseases that are considered primarily muscular in character. As they expressed it, "the eight most distinctive" clinical neural diseases of a group of over 50 that have been described are as follows:

1. Infantile muscular atrophy (Werdnig-Hoffman)
2. Familial spastic paralysis (Struempell, Freud, Jendrassik)
3. Hypertrophic neuritis (Dejerine-Sottas)
4. Peroneal muscular atrophy (Charcot-Marie-Tooth)
5. Familial areflexia (Roussy-Levy)
6. Spinal ataxia (Friedreich)
7. Cerebellar ataxia (Marie) with or without optic atrophy
8. Optic atrophy (Leber) with No. 2, 3, and 4.

The authors list a variable sporadic admixture of deafness, pupillary areflexia, retinitis pigmentosa, pes cavus, scoliosis, epilepsy, and dementia with these disorders.

Whether one regards 8 syndromes excessive or 50 insufficient, these authors state that the 8 embody combinations of 14 lesions occurring as follows:

(*a*) Retinal degeneration
(*b*) Optic atrophy
(*c*) Midbrain lesion with pupillary dysreflexia
(*d*) Midbrain lesions with progressive ophthalmoplegia externa
(*e*) Cerebellar atrophy involving the nuclei
(*f*) Pontile atrophy
(*g*) Olivary atrophy
(*h*) Cochlear degeneration
(*i*) Degeneration of dorsal tracts of cord
(*j*) Degeneration of spinocerebellar tracts
(*k*) Pyramidal tract degeneration
(*l*) Ventral horn-cell injury
(*m*) Radicular neuropathy
(*n*) Hypertrophic neuropathy

We submit, therefore, rather than creating a new name, eponym, category, or classification for the peculiar combination of degenerative lesions produced in this family, that it could be coded according to the Cobb and Bereday schema as follows: Familial Degenerative Disease of the Nervous System (6, 7, 8; *a*, *b*, *e*, *f*, *g*, *i*, *j*).

Summary

A description is made of four cases of heredofamilial ataxia associated with optic atrophy, occurring in four of the six male members of a family. The important clinical features are progressive blindness, cerebellar ataxia, generalized incoordination, dilated pupils, exaggerated facial movements, hyperactive tendon reflexes going on to spontaneous clonic muscular contrac-

tions, and, finally, emaciation. Necropsy of two patients revealed degenerative lesions of the optic system, the olivopontocerebellar regions, as well as the dorsal columns and spinocerebellar tracts.

The recent family tree is shown, with only one suggestion of a genetic source. The disease has appeared in one member of the family during adult life, in two during adolescence, and in one as a child.

The views of recent authors that the primary ataxias and the optic atrophies are variants of a hereditary predisposition to central nervous system degeneration are confirmed and extended. This family has accurately reproduced the clinical pattern of the disorders in all its affected members.

It is noted that the classification of Cobb and Bereday of the heredofamilial diseases of the nervous system is convertible to a code for accurately designating the clinical and anatomic features of these maladies.

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Pressor and Diminished Local Vasoconstrictor Effects of Levarterenol-Phentolamine Mixtures

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Levarterenol (*l*-norepinephrine [Levophed]) bitartrate is one of the most commonly used pressor amines in the treatment of shock. However, a major disadvantage is the development of ischemic necrosis in areas of accidental extravasation. On the basis of clinical use, starting in 1954, it was demonstrated by one of us [1] that, in such areas, the local vasoconstrictor effect could be counteracted by phentolamine (Regitine) methanesulfonate, an antiadrenergic drug. When 5-10 mg. of the latter drug, diluted in 20 cc. of water, was infiltrated subcutaneously throughout the area of ischemia, the pallor and coldness disappeared within five to seven minutes. Untreated areas became necrotic. Similar observations have been made by McGinn and his co-workers,[2] who added hyaluronidase to the phentolamine solution. Pelner [3] cited a case in which hyaluronidase favored the spread of ischemia. He also reported that another antiadrenergic drug, piperoxan (Benodaine), had an action similar to that of phentolamine.

In an experimental study, using the shaved abdomens of rabbits, one of us [1] demonstrated that 1 mg. of levarterenol (1 mg. in 1 cc.) injected intracutaneously produced a localized ischemic wheal, which regularly became necrotic within 24 hours. This ischemic necrosis could be prevented by the injection into the wheal of 1 mg. of phentolamine simultaneously with or up to six hours after the injection of levarterenol. No protection was observed if 24 hours elapsed before the use of phentolamine.

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The most important factors in the successful prevention of ischemic necrosis have been the early detection and treatment of levarterenol extravasation. Prompt detection requires frequent and careful inspection of the injection site. Unfortunately, careful supervision is all too often not available.

The problem could be solved if there were available a substance which, added to the levarterenol infusion, would antagonize its local vasoconstrictor action but not its systemic pressor effect. Phentolamine has the former property, but little was known of its effect upon the blood pressure in man during prolonged intravenous administration.

We decided to administer phentolamine * simultaneously with levarterenol.† In this manner, the ischemic effects from the extravasation of levarterenol could be counteracted by the simultaneous infiltration of phentolamine. The protection offered by phentolamine would be automatic. Observations on the pressor effect of such mixtures could also be made in the course of such a study.

The purpose of this paper is to present our observations on (1) the pressor effect of levarterenol-phentolamine mixtures in normotensive patients, (2) the local vasoconstrictor effect of subcutaneous infiltration of such mixtures, and (3) preliminary experiences with the use of such mixtures in the treatment of shock.

* Regitine, supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

† Levophed, supplied by Winthrop Laboratories, New York.

Method

Intravenous infusions were made into a suitable vein of the hand, forearm, or antecubital fossa with the use of a 20 gauge, 1½ in. needle. All doses of levarterenol and phentolamine were diluted in 1,000 cc. of 5% dextrose in water. The solutions were administered at varying rates, depending upon the pressor effect desired.

Results

1. *Comparison of Pressor Effect of Levarterenol and Mixtures of Levarterenol and Phentolamine in Normotensive Adults*

Case 1.—A 60-year-old man with multiple sclerosis was admitted in October, 1957. Control blood pressure was 105/65. A solution containing 4 mg. of levarterenol, administered intravenously at 28 drops per minute, elevated the blood pressure to 155/80. The blood pressure remained elevated despite the progressive addition of 4, 14, and 24 mg. of phentolamine to the infusion.

Case 2.—A 42-year-old man with multiple myeloma was admitted in October, 1957. Control blood pressure was 115/70. It was raised to 170/95 by a solution containing 4 mg. of levarterenol, given at 20 drops per minute. The addition of 20 mg. of phentolamine to the flask did not alter the pressor effect.

Case 3.—A 55-year-old man was admitted in May, 1958, with purpura. Control blood pressure was 120/75. It was elevated to 180/100 by an intravenous drip of 4 mg. of levarterenol and 10 mg. of phentolamine, given at 28-32 drops per minute. The progressive addition of phentolamine up to 40 mg. did not alter the pressor effect. However, with 60 mg. of phentolamine the pressor effect decreased during a 50-minute period of administration. At this point, four hours after the start of the experiment, levarterenol alone, given at 56 drops per minute, raised the blood pressure to 180/90. At 28 drops per minute, the blood pressure rose to only 145/80 (Fig. 1). Two weeks later, a solution containing 4 mg. of levarterenol, given at 28 drops per minute, again raised the blood pressure to 180/100. The immediate addition of 60 mg. of phentolamine to this solution did not alter the pressor effect during a period of 20 minutes.

Case 4.—A 22-year-old man, convalescing from acute brucellosis, was admitted in February, 1958. Control blood pressure was 125/70. It was raised to 170/80 by a solution of 4 mg. of levarterenol, given at 80 drops per minute. The progressive addition to this infusion of increments of 10 mg. of phentolamine up to a total of 60 mg. did not reduce the pressor effect of levarterenol. On another day, the blood pressure was raised to 168/80 with a mixture of 4 mg. of levarterenol and 10 mg. of phentolamine, given at 88 drops per minute. While the infusion was continued in one arm, a rapid intravenous injection of 5 mg. of phentolamine in 1 cc. of saline was given in the opposite arm. The blood pressure dropped to 145/30 in two minutes and returned to 165/80 five minutes after the injection (Fig. 2).

Case 5.—A 20-year-old man was convalescing from infectious hepatitis in December, 1957. Blood pressure was 145/80. It was raised to 180/115 with a solution of 4 mg. of levarterenol and 10 mg. of phentolamine, given at 40 drops per minute. While the injection was continued in one arm, a rapid intravenous injection of 5 mg. of phentolamine in 1 cc. of saline in the opposite arm reduced the blood pressure to 165/75 within 30 sec-

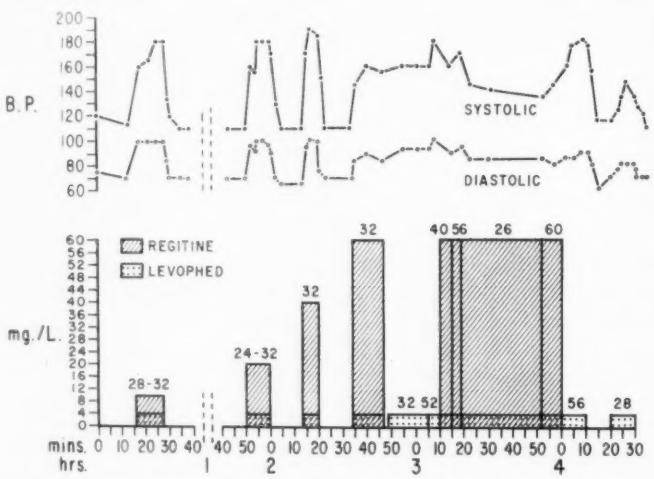

Fig. 1 (Case 3).—The pressor effects of mixtures of levarterenol (Levophed) and phentolamine (Regitine) in a normotensive patient. The numbers on the top of the bars indicate drops per minute.

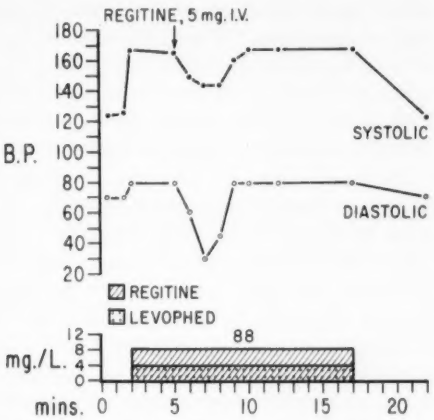

Fig. 2 (CASE 4).—The effect of a rapid intravenous injection of 5 mg. of phentolamine (Regitine) on hypertension produced by a levarterenol-phentolamine (Levophed-Regitine) mixture.

onds. It returned to 170/100 seven minutes later and remained elevated while the levarterenol-phentolamine mixture was continued for another hour. Discontinuation of this infusion caused the blood pressure to return to 140/70.

2. Local Vasoconstrictor Effect of Subcutaneous Infiltrations of Levarterenol-Phentolamine Mixtures

Five critically ill patients were studied. The observations were similar in all cases. Subcutaneous infiltrations of from 50-150 cc. of a solution of 4 mg. of levarterenol in one hand or forearm caused a localized ischemic area, which persisted or which disappeared only after two to three hours. In contrast, similar infiltrations of mixtures of 4 mg. of levarterenol and 5-24 mg. of phentolamine into the opposite hand or forearm produced only slight vasoconstriction, lasting 15-30 minutes. An illustrative case is presented.

CASE 6.—An 80-year-old man was admitted in October, 1957, with a right hemiplegia in coma. A total of 150 cc. of a solution of 4 mg. of levarterenol was slowly infiltrated subcutaneously into the dorsum of the right hand. This area became pale, mottled, and cold. No lessening or spread of the ischemic infiltration was noted after 20 minutes. To prevent necrosis, 5 mg. of phentolamine, dissolved in 20 cc. of isotonic saline, was injected subcutaneously at several sites in the ischemic area. It became warm and pink within five minutes. No necrosis developed. To compare the patient's response to a mixture of levarterenol and phentolamine, 150 cc. of a solution of 4 mg. of levarterenol and 24 mg. of phentolamine was injected subcutaneously into the dorsum of the left hand over a period of 30 minutes. The area of infiltration, though initially cool but not mottled, became warm within 15 minutes and diffused up to the elbow within 30 minutes. No ischemia was observed. On subsequent days, additional observations were made with use of mixtures containing 4 mg. of levarterenol and 5 or 10 mg. of phentolamine. In both instances, the local infiltration began to disappear within 20 minutes. No ischemia developed.

3. Treatment of Shock with Mixtures of Levarterenol and Phentolamine

CASE 11.—A 33-year-old woman was admitted in December, 1957, in coma and shock due to acute barbiturate poisoning. Blood pressure was 60/40, later falling to 30/0. An intravenous infusion containing 4 mg. of levarterenol, given at 28 drops per minute, raised the blood pressure to 120/80. Cessation of the infusion caused a prompt drop of the

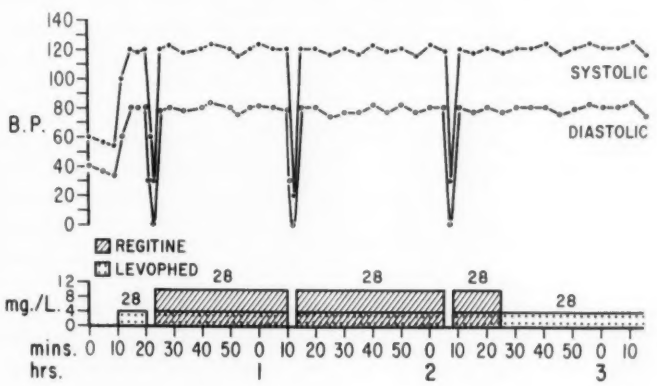

Fig. 3 (CASE 11).—Treatment of shock with levarterenol (Levophed) and a levarterenol-phentolamine (Levophed-Regitine) mixture at 28 drops per minute.

blood pressure. It was restored to normal by an infusion containing 4 mg. of levarterenol and 10 mg. of phentolamine, given at 28 drops per minute. This mixture was used successfully for over two hours. The original solution of 4 mg. of levarterenol alone was then substituted. The same pressor effect was observed for eight hours. The patient was then able to maintain her own blood pressure without pressor drugs. She made a full recovery (Fig. 3).

Case 12.—A 31-year-old man with acute lymphosarcoma was admitted in November, 1957. He was terminal and in shock, with a blood pressure of 50/10. A solution of 8 mg. of levarterenol, given at 36 drops per minute, maintained the blood pressure at 85/20. The same blood pressure was maintained with an infusion of 4 mg. of levarterenol and 10 mg. of phentolamine. However, the state of shock gradually worsened in spite of increasing amounts of levarterenol. The patient died after three hours.

Case 13.—A 51-year-old man was admitted in December, 1957, with an acute myocardial infarction and shock. His blood pressure was 95/85. A solution of 4 mg. of levarterenol raised his blood pressure to 115/90. The addition of 10 mg. of phentolamine did not reduce the pressor effect. After 24 hours, the patient was able to maintain his blood pressure without the mixture. He later died as a result of ventricular fibrillation.

Case 14.—A 67-year-old woman was admitted in February, 1958, with long-standing arteriosclerotic heart disease, auricular fibrillation, and congestive heart failure. She went into shock after an operation for an incarcerated inguinal hernia. Her blood pressure of 80/60 was elevated to 110/80 with an infusion containing 4 mg. of levarterenol. The addition of 5 mg. of phentolamine did not reduce the pressor effect. Her pressure was maintained with this solution until her death, 24 hours later.

Case 15.—A 54-year-old woman was admitted in February, 1958, with a thrombotic occlusion of the bifurcation of the aorta. Resection of the lower abdominal aorta and common iliac arteries was performed, and a synthetic prosthesis was inserted. The patient went into shock postoperatively, with a blood pressure of 70/60. A solution of 8 mg. of levarterenol and later 4 mg. of levarterenol maintained the pressure at 130/80. When 5 mg. of phentolamine was added to the infusion, there was no reduction in the pressor effect. The patient's blood pressure was maintained with this mixture for 38 hours. She died in severe toxemia due to gangrene of both lower extremities.

Comment

These studies have demonstrated that solutions of levarterenol to which relatively large amounts of phentolamine have been added have a pressor effect equivalent to that of levarterenol alone. This would appear to be a paradox, considering the antiadrenergic properties of phentolamine. The explanation can be found in the dosage and pharmacological action of phentolamine.

Five normotensive patients received mixtures containing 4 mg. of levarterenol and from 10-60 mg. of phentolamine. The mixtures were administered intravenously in a liter of 5% dextrose in water at rates varying from 24 to 88 drops per minute. Phentolamine in doses of 10-40 mg. per liter did not decrease the pressor effect of 4 mg. of levarterenol. However, 60 mg. of phentolamine decreased, but did not abolish, the hypertension produced by 4 mg. of levarterenol. At this dosage level, the antipressor effect appeared to be cumulative with prolonged administration (Fig. 1).

Two of the five normotensive patients, who were made relatively hypertensive by a continuous intravenous drip of a levarterenol-phentolamine mixture, also received a rapid intravenous injection of 5 mg. of phentolamine. The technique was essentially that of a "phentolamine test" for pheochromocytoma. The response consisted of a rapid drop of both systolic and diastolic blood pressure that lasted five minutes in one case and seven minutes in the other. These observations serve to demonstrate that 5 mg. of phentolamine injected intravenously within a few seconds is sufficient to antagonize briefly the pressor effect of a slow drip of 4 mg. of levarterenol and 10 mg. of phentolamine. We did not attempt to determine the amount of phentolamine necessary to completely abolish the pressor effect of 4 mg. of levarterenol.

Additional information obtained from laboratory studies has confirmed the feeble effect of phentolamine against the pressor action of levarterenol. The original experiments in dogs, performed in 1949, disclosed that even after as much phentolamine as 13 mg. per kilogram of body weight, levarterenol still caused a slight elevation of blood pressure. On the other hand, its

action against *l*-epinephrine was very potent. Phentolamine, in a dose of only 1.8 mg. per kilogram of body weight, not only abolished the pressor effect of *l*-epinephrine but also produced *l*-epinephrine reversal.[4] In more recent studies, Schmitt[5] obtained essentially the same results. He showed that 10 times the dose of phentolamine that abolished *l*-epinephrine hypertension was required to block levarterenol hypertension in dogs.

In contrast to its weak effect against levarterenol-induced hypertension, phentolamine has a potent effect against the local vasoconstrictor properties of both levarterenol and *l*-epinephrine. Johnson, Green, and Lanier[6] demonstrated in dogs that 0.3 mg. of phentolamine per kilogram of body weight, injected intra-arterially, blocked the vasoconstrictor effect of 1μg. of both *l*-epinephrine and levarterenol. These observations were true for blood flow through both the muscle and skin of the hind limbs of dogs. Observations such as these suggest that relatively small doses of phentolamine could be effective in preventing local ischemia in areas of levarterenol extravasation. In rabbits, 1 mg. of phentolamine injected into an ischemic intracutaneous wheal produced by 1 mg. of levarterenol prevented necrosis.[1] In patients in shock, 5 mg. of phentolamine has neutralized the local vasoconstrictor effect of as much as 1.8 mg. of levarterenol.[1]

Our observations in five patients suggest that doses of phentolamine that do not decrease the pressor effect of levarterenol do combat its local vasoconstrictor action. Subcutaneous infiltrations of 50-150 cc. of mixtures, containing 4 mg. of levarterenol and 5-40 mg. of phentolamine per liter were less blanched and disappeared more rapidly than did similar infiltrations of levarterenol alone. One patient (Case 6) is cited in whom the area infiltrated with levarterenol became so ischemic that necrosis might have developed. The local injection of 5 mg. of phentolamine promptly abolished the vasoconstriction. In contrast, the area on the opposite hand, into which a mixture of 4 mg. of levarterenol and 5, 10, or 24 mg. of phentolamine was infiltrated, showed slight pallor, which disappeared spontaneously in 20-30 minutes.

The data collected from five patients in shock are of special interest. They clearly demonstrated that levarterenol phentolamine mixtures have a pressor effect in shock equal to levarterenol alone. The first patient (Case 11), with acute barbiturate poisoning, responded as well to a mixture of 4 mg. of levarterenol and 10 mg. of phentolamine as to levarterenol alone. The mixture was successfully used for a period of two hours. Levarterenol alone was administered for the subsequent six hours. The patient ultimately recovered (Fig. 3). Case 12 was in shock with a terminal lymphosarcoma. A levarterenol-phentolamine mixture (4:10 mg.) produced the same pressor response as 8 mg. of levarterenol alone. Case 13 was in mild shock due to an acute myocardial infarction. His blood pressure was maintained at normal levels for 24 hours with a mixture of 4 mg. of levarterenol and 10 mg. of phentolamine. Case 14 was a severe cardiac with congestive heart failure, auricular fibrillation, and shock following an operation for incarcerated inguinal hernia. Blood pressure was raised and maintained with a levarterenol-phentolamine mixture (4:5 mg.) for a period of 24 hours, until her death. Case 15, suffering from a thrombosis at the bifurcation of the aorta, was in shock after a resection. Her blood pressure was satisfactorily maintained for 38 hours with a mixture of 4 mg. of levarterenol and 5 mg. of phentolamine. She subsequently died of gangrene.

The possibility that phentolamine was inactivated in dilute solutions of levarterenol was considered. Should such chemical neutralization or deterioration take place, it might explain the unaltered pressor effect of levarterenol-phentolamine mixtures. Studies made for us disclosed that no such change took place. Phentolamine was stable

in solution with levarterenol in a ratio of 5:1 (20 mg. of phentolamine and 4 mg. of levarterenol) for 24 hours in 1 liter of 5% dextrose and water or 5% dextrose and saline.‡

Two details of the problem are under further study. One is to determine whether the routine use of levarterenol-phentolamine mixtures in a larger series of patients will regularly prevent ischemic necrosis at sites of accidental extravasation. The second is an experimental study on rabbits to establish the smallest dose of phentolamine which will be effective against varying doses of levarterenol.§

Summary

Mixtures of levarterenol (*l*-norepinephrine [Levophed]) and phentolamine (Regitine) in ratios of 4:5 mg. up to 4:40 mg. per liter have the same pressor effect as levarterenol alone in normotensive patients. These same mixtures produce less vasoconstriction than levarterenol when infiltrated subcutaneously. Five patients in shock showed pressor effects from mixtures of 4 mg. of levarterenol and 5-10 mg. of phentolamine equivalent to that of levarterenol alone. In view of our findings, and if others have the same experience, it might be well to adopt the mixture of levarterenol and phentolamine as a routine procedure for the treatment of shock.

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‡ Information supplied by W. J. Mader and S. E. Slack, of the Research Department, Ciba Pharmaceutical Products, Inc.

§ Since the completion of this manuscript, 65 additional cases of shock have been treated with varying mixtures of levarterenol and phentolamine. Twenty-seven extravasations have occurred without any evidence of ischemic necrosis. Experiments on 36 rabbits demonstrated that as little as 2.5 mg. of phentolamine prevented necrosis invariably produced by solutions containing 8, 16, or 32 mg. of levarterenol per liter.

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Case Reports

Renal Tubular Acidosis

The Role of Defective Renal Tubular Sodium Reabsorption and Secondary Hyperaldosteronism in Its Pathogenesis

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In 1946, Albright et al.[1] described the disorder of "renal acidosis resulting from tubular insufficiency without glomerular insufficiency." Since then a number of reports and reviews of this condition have appeared under a variety of titles, such as renal acidosis, renal hyperchloremic acidosis, and renal tubular acidosis.[2-6]

The clinical features may be polyuria and polydipsia; the presence of renal calculi, muscular weakness, paralysis, or cramps due to hypokalemia, and bone pains resulting from osteomalacia. The diagnosis depends upon the presence of a systemic acidosis, manifested by a low blood pH, hyperchloremia and a low CO_2 content, and the excretion of a dilute urine that is alkaline or only slightly acid. A striking contrast exists between the degree of systemic acidosis and the high urinary pH. Hypokalemia is usually present. Nephrocalcinosis and osteomalacia are frequently encountered.

Theories regarding the etiology and pathogenesis of renal tubular acidosis include infection, impaired ammonia secretion,[1] inhibition of carbonic anhydrase,[7] sulfonamide toxicity,[8] and a congenital tubular defect.[5]

In a study of a patient with this disease, the possibility of increased aldosterone production was entertained because of the presence of marked hypokalemia. The salivary sodium and potassium concentrations were determined, and the results favored an increased production of aldosterone, which was confirmed by urinary assay. This increased aldosterone production was considered to be secondary to excessive renal sodium loss, a defect which appears to be responsible for the biochemical and clinical features of renal tubular acidosis.

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Report of Case

In March, 1949, a 35-year-old unmarried white woman was seen because of an attack of abdominal pain and vomiting, and an x-ray examination of the abdomen revealed the presence of bilateral nephrocalcinosis. The year before she had had influenza which was treated with sulfadiazine. For the past 15 years she had voided excessive quantities of urine and had suffered from extreme thirst, drinking as many as 10 pt. of fluid in a day. There had been previous attacks of unexplained abdominal pain and occasional pains in the loins and calves. Physical examination showed a thin woman (weight, 110 lb.; height, 5 ft. 2½ in.) in no apparent distress. No abnormal physical signs were detected, and the blood pressure was 135 mm. Hg systolic and 85 diastolic. A catheter specimen of urine contained a trace of albumin, numerous pus cells and Escherichia coli. The specific gravity of a morning specimen of urine was 1.005. The phenolsulfonphthalein test showed 21% excretion in 15 minutes and 60% in 2 hours. An x-ray examination of the skelton was normal. Findings on examination of the blood were as follows: urea, 25 mg. %; inorganic phosphorus, 2.6 and 2.8 mg. %; calcium, 9.8 and 10.2 mg. %; alkaline phosphatase, 10.2 and 11.2 King-Armstrong units %; chloride, 105 mEq. per liter; CO_2-combining power, 24 mEq. per liter; albumin, 4.6 gm., and globulin, 3.3 gm. %. Because of the coexistence of nephrocalcinosis, polyuria, and polydipsia and despite the absence of significant acidosis, the patient was considered to be suffering from renal tubular acidosis, a diagnosis which was

subsequently substantiated. On June 29, 1949, 16 gm. of citric acid, 12 gm. of sodium citrate, and 1 gm. of calcium gluconate, daily, were prescribed. On July 22, the blood urea was 49 mg. %; inorganic phosphorus, 3.1 mg. %; alkaline phosphatase, 6.5 King-Armstrong units %; chloride, 98 mEq. per liter; sodium, 142 mEq. per liter, and CO_2-combining power, 27 mEq. per liter. The urine did not contain an excess of amino acids. On two consecutive days in February, 1950, the 24-hour output of urine was 6,700 ml. and 6,500 ml., respectively. At about this time the patient discontinued her treatment, and she was not seen again until four years later.

In January, 1954, she again sought medical advice because of swollen ankles and a painful rash on the shins, the polyuria and polydipsia having continued unabated since 1950. Penicillin and, later, erythromycin were prescribed, and she was able to resume her occupation as a typist in two weeks but a few days later was obliged to return to bed because of extreme muscular weakness, breathlessness, tingling of the hands and feet, cramps in the calves, severe headache, thirst, and polyuria. She was unable to sit up unaided; her grip was weak; the tendon reflexes were abnormally brisk; her extremities were cold, and her respirations were deep. The blood urea was 75 mg. %; inorganic phosphorus, 4.4 mg. %; calcium, 8.6 mg. %; chloride, 120 mEq. per liter; sodium, 150 mEq. per liter; potassium, 2.3 mEq. per liter, and CO_2-combining power, 6.2 mEq. per liter. A diagnosis of hypokalemic paralysis was made, and a mixture of 2 gm. of postassium citrate, 2 gm. of potassium chloride, and 2 gm. of potassium bicarbonate, three times daily, was prescribed. Within a few hours, her muscular power had improved and by the next day was normal. X-ray studies again showed nephrocalcinosis and a normal skeleton. Two weeks later the blood urea was 29 mg. %; chloride, 110 mEq. per liter; sodium, 151 mEq. per liter; potassium, 4.2 mEq. per liter, and CO_2-combining power, 19 mEq. per liter. A daily maintenance dose of 6 gm. of potassium citrate was prescribed.

On April 10, 1954, she was readmitted to the hospital, complaining of intermittent pain and swelling of the ankles, which disappeared after a few days. In order to test the need for continued potassium therapy, the supplements of potassium were withheld. In 10 days the serum potassium level fell from 4 to 2.8 mEq. per liter, and the blood urea rose from 38 to 100 mg. %, with recurrence of breathlessness and weakness. These symptoms were promptly relieved when potassium therapy was resumed, and she was discharged on a daily maintenance dose of 1.5 gm. of potassium citrate and 1.5 gm. of potassium bicarbonate, which she continued to take for the following two and one-half years. In February, 1956, the 24-hour urinary excretion of 17-hydroxycorticosteroids was 9.2 mg. (normal, 6.6-3.7) and of 17-ketosteroids 4.2 mg. (normal, 5-10 mg.). The continuously high urinary output was uninfluenced by the administration of vasopressin (Pitressin).

In March, 1956, the possibility was entertained that the hypokalemia might be the result of excessive aldosterone production, but facilities for direct assay were not available locally. Since the production of excess aldosterone may be reflected in a high-potassium and a low-sodium concentration in the saliva,[9] the patient was studied from this point of view and a series of six such determinations carried out. The concentration of potassium was found to be high (mean, 34.1 mEq. per liter; range, 32.4-36 mEq. per liter) and that of sodium low (mean, 2.9 mEq. per liter; range, 1.7-4.3 mEq. per liter). In 22 normal subjects the mean salivary potassium concentration was 16.7 mEq. per liter (range 9.5-20.4 mEq. per liter) and the mean salivary sodium concentration 6.2 mEq. per liter (range, 2.4-16.3 mEq. per liter). As these results were indicative of excess aldosterone production it was considered necessary to seek confirmation by direct assay. A 24-hour specimen of urine was thereupon extracted, frozen and dispatched by air transport to S. A. Simpson and J. F. Tait, at the Middlesex Hospital, London, England, for aldosterone assay.* This specimen contained 44μg. of aldosterone (mean normal, 10.5μg., range 5μg.-22μg.), 25μg. of hydrocortisone (mean normal, 38μg., range 15μg.-88μg.), 143 mEq. of sodium, and 52 mEq. of potassium.

The increased aldosterone excretion led us to determine the ability of the patient's renal tubules to conserve sodium, for sodium conservation would be impaired were the hyperaldosteronism secondary to renal dysfunction but retained in primary aldosteronism. In October, 1956, the patient was admitted to the hospital in order to observe the effects of sodium deprivation.

The biochemical findings on admission were as follows: blood urea, 63 mg. %; inorganic phosphorus, 4.8 mg. %; calcium, 9 mg. %; chloride, 98 mEq. per liter; sodium, 140 mEq. per liter; potassium, 3.9 mEq. per liter, and CO_2-combining power, 17 mEq. per liter. Her supplements of potassium were discontinued, and three days later a diet low in sodium (6 mEq. per 24 hours) was started and continued for five days. On the second day, the urinary sodium decreased from 173 to 71 mEq. per 24 hours, but it fell no lower than 61 mEq. by the fifth day (Table). On the third day, marked deterioration in the patient's condition occurred. There was increased thirst, weakness, inability to concentrate, irritability, cramps, and

* The assay was arranged on our behalf by Dr. J. D. N. Nabarro, Middlesex Hospital, London.

Response to Sodium Deprivation

Date	Urinary Sodium, mEq/24 Hr.	Urinary Potassium, mEq/24 Hr.	Blood Urea, Mg. %	Remarks
10/6/56	199	39	63	Potassium supplements discontinued
10/7/56	186	53	—	—
10/8/56	173	58	—	—
10/9/56	136	49	—	Sodium-poor diet (6 mEq/24 hr.) started
10/10/56	71	47	—	—
10/11/56	68	54	—	—
10/12/56	64	57	—	Cramps, Irritability
10/13/56	61	58	136	Weakness, Breathlessness

breathlessness, and these symptoms became progressively more pronounced during the remaining two days of the test period, at the end of which the findings on blood analysis were as follows: urea, 136 mg. %; chloride, 92 mEq. per liter; sodium, 133 mEq. per liter; potassium, 3.2 mEq. per liter; and CO_2-combining power, 13 mEq. per liter.

On the day following the period of sodium deprivation, the patient developed severe unexplained diarrhea, nausea, and a shock-like state, which lasted five days and necessitated the use of intravenous fluid therapy and hydrocortisone. The serum potassium fell to 2.8 mEq. per liter and the blood urea remained at high levels—110 and 108 mg. %. Five days after the diarrhea had ceased, the blood urea was 34 mg. %; chloride, 102 mEq. per liter; sodium, 139 mEq. per liter; potassium, 3.9 mEq. per liter, and the CO_2-combining power, 23 mEq. per liter.

We concluded that the hyperaldosteronism was, in fact, secondary to impaired sodium conservation, approximately 400 mEq. of sodium having been lost in the urine during five days of sodium deprivation. In view of this, it was anticipated that the hypokalemia which resulted from excessive secretion of aldosterone secondary to renal sodium loss might be controlled by the addition of sodium supplements alone. This therapeutic approach was adopted, and daily supplements of 4 gm. of sodium bicarbonate and 4 gm. of sodium citrate were prescribed.

Despite continued thirst and polyuria the patient improved considerably. She has become more energetic and is able to walk long distances without tiring; her breathlessness and cramps have disappeared, and she has gained weight. After six months of this therapy the salivary potassium concentration was 24 mEq. per liter and a further six months later again 24 mEq. per liter; concentrations distinctly lower than those obtained prior to sodium supplementation and suggestive of a diminution in aldosterone activity. In September, 1957, the urea was 35 mg. %; chloride, 106 mEq. per liter; sodium, 139 mEq. per liter; potassium, 3.6 mEq. per liter, and CO_2-combining power, 24 mEq. per liter.

This clinical improvement was maintained. However, it was thought that excessive sodium loss would persist and prevent full repletion of body sodium. In consequence, increased aldosterone secretion would continue to cause increased potassium loss although to less extent. Accordingly, on this theoretical basis, potassium supplements were added, but it is noteworthy that no further clinical improvement ensued.

Comment

In a patient with renal tubular acidosis the possibility was investigated that the hypokalemia was due to increased secretion of aldosterone. Estimation of salivary sodium and potassium concentrations showed low sodium and high potassium values compared with control subjects. These results were in keeping with increased aldosterone production[9] and were not explicable on the basis of a simple renal leak of potassium. Urinary assay confirmed the presence of increased quantities of aldosterone.

Although the precise stimulus or stimuli for aldosterone secretion are still under investigation,[10,15] an important one appears to be a reduction in the volume of the extracellular fluid compartment. As this volume is primarily dependent on the amount of sodium present, sodium depletion would result in its reduction and consequently in increased aldosterone secretion.

It was postulated that the basic lesion in our patient was an impairment of the normal renal sodium-conservation mechanism and that the hyperaldosteronism was secondary to this. In order to test this hypothesis she was given a diet low in sodium for five days. Her total daily urinary sodium fell from 173 to 71 mEq. after two days on this diet but fell no lower than 61 mEq. by the fifth day. This is in contrast to the effect of sodium deprivation in normal subjects, in whom sodium virtually disappears from the urine in a few days. When con-

sidered against the background of an initially high aldosterone level in the urine and the sodium conservation by the salivary glands, this failure of renal sodium conservation is even more striking.

This sodium loss could result from a lesion of either the proximal or the distal tubules. Normally about 80% of the sodium in the glomerular filtrate is reabsorbed at the proximal tubule and the remaining 20% reaches the distal tubule, where a further variable amount is reabsorbed. Aldosterone plays a major role in mediating this process. It is suggested that in our patient there is impaired sodium reabsorption at the proximal tubule and that the increased secretion of aldosterone which is provoked thereby partially compensates by more effective sodium reabsorption at the distal tubule.

Another possible explanation for the impaired renal conservation of sodium in the presence of increased production of aldosterone is that the renal tubules are relatively insensitive to aldosterone. Such end-organ resistance should give rise to a state of progressive sodium depletion resembling Addison's disease, which was not the case in our patient. Moreover, the hypokalemia indicated a normal secretory response by the distal tubules to aldosterone, thus rendering the possibility of end-organ resistance even less likely. It should be possible to distinguish renal loss of sodium with consequent hyperaldosteronism from end-organ resistance to aldosterone by the administration of Amphenone (a diphenyl compound). This substance, because of its aldosterone-inhibiting properties,[15] would be expected to bring about deterioration in the case of the former condition but not in the case of the latter.

The finding of impaired renal sodium conservation is in conformity with Bartter's suggestion[16] that some patients with so-called "potassium-losing" nephritis are, in fact, sodium losers in whom secondary aldosteronism has stimulated the exchange of sodium for potassium by the distal tubules. It is also in keeping with Berliner's observation[17] that in renal acidosis potassium excretion can be markedly reduced by the administration of sodium bicarbonate. Furthermore, Smith and Schreiner[18] have shown that in this condition the total body sodium is at the lower range of normal.

In the light of the foregoing, it would appear that impaired sodium reabsorption by the proximal renal tubules is the underlying defect which initiates a series of biochemical events responsible for the various manifestations of renal tubular acidosis. The increased aldosterone secretion resulting from this mechanism gives rise to excessive potassium secretion by the distal tubules, with consequent depletion of body potassium. Normal reabsorption of chloride in the face of decreased sodium reabsorption gives rise to hyperchloremia. The already-diminished amount of sodium available for bicarbonate is further reduced by this hyperchloremia, and acidosis results. The increased secretion of potassium partially displaces the secretion of hydrogen ions into the tubular lumen, hence the tendency for an alkaline urine. The high urinary pH causes a reduction in the amount of urinary ammonia, since the production and diffusion of ammonia is stimulated by the hydrogen ion concentration of the urine.[19,20] The vasopressin-resistant polyuria could be due to a hypokalemic nephropathy or to impaired water reabsorption accompanying the impaired sodium reabsorption by the proximal tubules.

Osteomalacia is a complication frequently encountered in renal tubular acidosis. Mahler and Stanbury[21] have suggested that the potassium depletion causes a decrease in the tubular reabsorption of phosphate, as a result of which excessive quantities of phosphate are lost in the urine, and osteomalacia ensues. An alternate explanation is that the acidosis which increases phosphate excretion is responsible. Osteomalacia does not appear to be a feature of primary aldosteronism where alkalosis rather than acidosis is associated with potassium depletion.

Accordingly, one may postulate that the acidosis gives rise to osteomalacia either by increasing phosphate excretion or by a direct effect on bone. Nephrocalcinosis would result from calcium precipitation in a relatively alkaline urine.

There are a number of syndromes in which there is defective transport of specific substances by the proximal tubules. Among these are the Fanconi syndrome,[22] cystinuria,[23] renal glycosuria, certain varieties of vitamin D-resistant rickets,[24] and glycosuria and amino-aciduria in combination.[25] It seems that renal tubular acidosis is yet another condition in which the function of the proximal tubule is impaired. These diseases are all considered to be genetically determined, and it is therefore noteworthy that in three recent reports of renal tubular acidosis reference is made to the familial incidence of the disease.[4-6]

Discussion of renal tubular acidosis of infancy[26] has purposely been omitted, since it is a somewhat different disorder of limited duration when adequately treated and displaying neither hypokalemia nor osteomalacia. It would be of interest to determine whether lack of sodium conservation occurs also in this disease. Similar studies in Fanconi's syndrome could ascertain whether the hypokalemia results from impaired potassium reabsorption by the defective proximal tubule or from a mechanism similar to the one suggested in our patient.

Summary

A patient with renal tubular acidosis, nephrocalcinosis, and hypokalemia is described.

High-potassium and low-sodium salivary concentrations were found to be present.

Excessive aldosterone secretion and impaired renal sodium conservation were demonstrated.

It is postulated that the whole clinical picture in renal tubular acidosis may be explained on the basis of impaired sodium conservation by the kidneys.

Dr. B. M. Bloomberg performed the biochemical investigations and Dr. M. Davimes and Dr. S. B. Z. Frame referred the patient. Miss P. L. Wills, Senior Dietitian, Johannesburg General Hospital, arranged the low-sodium diet.

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Leukemoid Reaction in Infectious Mononucleosis

An Infrequent Manifestation Simulating Leukemia

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Infectious mononucleosis, a common disorder in the young-adult age group, is well known for its protean features. Leukemia may be suggested when bleeding manifestations, thrombocytopenia, and hemolytic anemia are found in association with lymphadenopathy and splenomegaly. The leukocyte count rarely exceeds 30,000 per cubic millimeter.[1] The following report is an example of infectious mononucleosis with the infrequent leukemoid response which may further mimic leukemia. The causes of a lymphocytic leukocytosis are reviewed.

Report of Case

The patient, an 18-year-old student, was admitted to the Peter Bent Brigham Hospital for the first time, on Nov. 20, 1956, because of fever of four days' duration. He had been well until nine days before entry, when sore throat, retro-orbital pain, and malaise began. Fever, headache, anorexia, nausea and vomiting, increasing malaise without chill, cough, chest pain, and gastrointestinal or genitourinary symptoms were noted during the four days before admission.

Initial physical examination showed an acutely ill young man with a temperature of 102 F, pulse of 96 per minute, and a blood pressure of 110/60. There were ecchymoses of both eyelids and a subconjunctival hemorrhage on the left and petechiae on the soft palate. The diffusely reddened pharynx was covered with a dry, white exudate. Generalized lymphadenopathy was present, with the posterior cervical nodes strikingly enlarged. The heart and lungs were normal. A minimally enlarged tender liver and an easily palpable, soft, tender spleen were noted. The remainder of the examination was normal.

Urinalysis and the blood serological test for syphilis were negative. The hematocrit was 44%; platelet count, 181,000 per cubic millimeter, and leukocyte count, 6,800 per cubic millimeter, with 7% neutrophils, 20% band forms, 1% eosinophils, 3% monocytes, and 49% mature and 20% atypical lymphocytes. The sedimentation rate was 7 mm. (Wintrobe); blood urea nitrogen, 12 mg. %; serum albumin, 3.8, and globulin, 2.4 gm. %, and fasting blood sugar 97 mg. %. Serum sodium was 139 mEq. per liter; potassium, 4.5 mEq. per liter; carbon dioxide, 18 mm. per liter, and chloride 106 mEq. per liter. Serum bilirubin was 0.5 mg. %; alkaline phosphatase, 2.2 Bodansky units, and the prothrombin activity, 35% of normal. There was 22% retention of sulfobromophthalein (Bromsulphalein). Initially the thymol turbidity was 19 units (normal, less than 40); this rose to a peak of 76 one week later and then gradually returned to normal. Stool was negative for occult blood. Blood cultures were negative; streptococci were cultured from nose and throat. The x-rays of chest and abdomen were normal, except for minimal splenomegaly. An electrocardiogram showed diffuse nonspecific T-wave changes consistent with a myocarditis; these returned to normal in two weeks.

The blood heterophil was postive in a dilution of 1:320. Cold agglutinins were present in a 1:10 dilution. Bone marrow showed normal granulocyte, erythrocyte, and platelet precursors and clumps of large histiocytes suggestive of early granuloma formation.

He continued acutely ill, with daily temperature rising to 103-104 F during the first week. Penicillin was given for a two-week period because of the streptococci. In the second week there was gradual defervescence, with commensurate clinical improvement. Pretibial petechiae appeared transiently during the second week, at a time when the platelet count was 126,000 per cubic millimeter, the prothrombin activity was 40% of normal, and the tourniquet test for increased capillary premeability was normal.

The leukocyte count rose progressively, as shown in the Figure, reaching a peak of 53,000 per cubic millimeter on the seventh hospital day,

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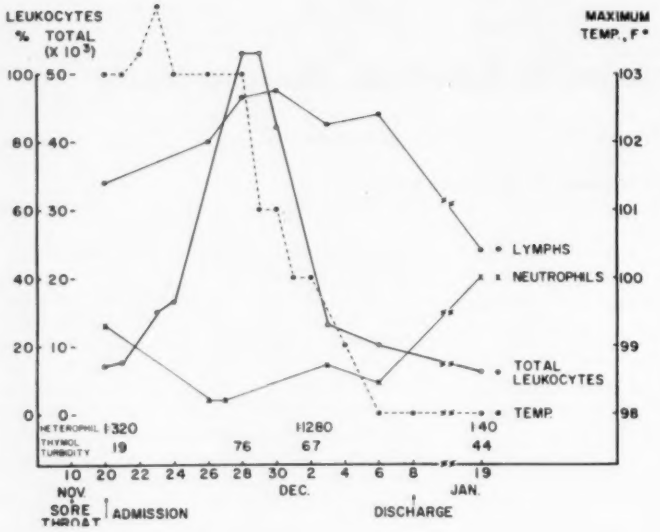

Clinical course and leukocytic response.

16 days after the onset of symptoms. This leukocytosis consisted almost entirely of lymphocytes. Differential counts showed 50% atypical lymphocytes, 42% mature lymphocytes, and 8% granulocytes.

He was discharged on Dec. 8, 1956. Severe asthenia gradually diminished over the following month, allowing him to resume studies three months after the onset of symptoms. Leukocyte counts have remained in the 6,000 to 8,000 range, with the differential showing a fall in lymphocytes and a rise in granulocytes. On Jan. 19, 1957, there were no demonstrable cold agglutinins, heterophil was positive in 1:40 dilution, and the 6,000 per cubic millimeter leukocyte count was associated with 48% lymphocytes, including 3% atypical forms, 45% mature granulocytes, and 7% monocytes. In May, 1957, he had returned to full activity; there was no residual adenopathy, and the spleen was not palpable.

Comment

The initial clinical and laboratory features of the patient reported were adequate to establish the diagnosis of infectious mononucleosis. The severity of the febrile course, the bleeding phenomena, the liver involvement, and the electrocardiographic evidence suggesting myocarditis were impressive although not unusual features of infectious mononucleosis.

The leukemoid response, consisting almost entirely of atypical lymphocytes, is an uncommon feature. This was transient, with the daily determined leukocyte count remaining over 40,000 per cubic millimeter for only three days. Wintrobe[1] states that the leukocyte count in patients with infectious mononucleosis rarely exceeds 30,000 per cubic millimeter. Bernstein,[2] in a review of 65 cases, noted a leukocyte count of over 30,000 per cubic millimeter in 1.5%, with the frequency distribution shown in Table 1.

Table 2 summarizes five reports of infectious mononucleosis in adults associated with leukocyte counts of over 30,000. Bernstein[2] cites several instances in children with counts as high as 63,000. As illus-

TABLE 1.—*Frequency Distribution of Leukocyte Count in Infectious Mononucleosis**

Maximal Leukocyte Count/Cu. Mm.	Frequency, %
6,000-8,000	7
8,000-10,000	25
10,000-15,000	39.5
15,000-20,000	22
20,000-25,000	3.5
25,000-30,000	1.5
Over 30,000	1.5

* Reproduced with permission from Bernstein, A.: *Medicine* 19:85-151 (Feb.) 1940; Baltimore, The Williams & Wilkins Company.

TABLE 2.—*Leukemoid Response in Infectious Mononucleosis in Adults*

Year	Author	Age of Patient	Maximal Leukocyte Count	Heterophil
1927	Potter [5]	47	60,000	
1933	Barnett [5]	22	49,000	
1934	Tidy [3]	"Adult"	33,000	
1935	McAlpin [5]	35	42,000	
1945	Press [4]	23	43,000	
1958	Shipp & Baden	18	53,000	1:1,280

[5] Cited by Bernstein.[2]

TABLE 3.—*Causes of Absolute Lymphocytosis* [1]

Infections	
Acute	Infectious mononucleosis, pertussis, acute infectious lymphocytosis, exanthems (especially mumps & rubella), during convalescence from acute infections
Chronic	Tuberculosis, brucellosis, secondary syphilis, infectious hepatitis
Neoplastic diseases	Metastatic malignancies (stomach, colon, lung, renal, adrenal), lymphoma, multiple myeloma
Lymphocytic leukemia	

[1] Modified from Wintrobe.[1]

trated by the present case, it is possible that a transient elevation of the leukocyte count occurs more commonly, being unrecognized unless frequent blood cell counts are done.

If a patient with infectious mononucleosis is seen with a lymphocytic leukocytosis and a negative heterophil agglutination test the differential diagnosis should include all the causes of lymphocytosis which are shown in Table 3. In the younger age group the major problem is the infectious group, especially acute infectious lymphocytosis. The latter benign condition, occurring mostly in children, is characterized by a transient symptomatic response; no adenopathy or splenomegaly; a leukocytosis (40,000 to 100,000 per cubic millimeter), consisting of small "adult" lymphocytes, which persists for three to seven weeks, and a uniformly negative heterophil agglutination test. The chronic infections constitute the significant consideration in the young adult because of the important therapeutic implications. Tuberculosis is the most important example. In older age groups the lymphocytosis may be indicative of underlying neoplastic disease.

An appreciation of the leukocyte response with infectious mononucleosis is important in understanding the natural history of this disorder. Of practical importance is the fact that an elevated leukocyte count in association with bleeding phenomena, adenopathy, splenomegaly, and anemia may simulate leukemia. The atypical lymphocytes may be confused with "blast" forms to further complicate the differential diagnosis.

Summary

An instance of infectious mononucleosis in an 18-year-old student associated with a transient leukemoid reaction (leukocyte count over 50,000 per cubic millimeter) is reported. The leukocytosis consisted largely of lymphocytes; many of the atypical lymphocytes simulated "blast" forms. This feature in a less characteristic clinical setting may suggest leukemia, especially when associated with bleeding manifestations, anemia, adenopathy, and splenomegaly. The causes of lymphocytic leukocytosis are reviewed.

Dr. Frank Gardner, Hematologist, Peter Bent Brigham Hospital, gave advice and criticism and did the interpretation of the bone marrow studies.

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A Note on Radiation Telangiectases

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A characteristic example of physical force causing injury to blood vessels in the skin is seen in the telangiectases which occur in the skin some time after heavy x-irradiation. I am not familiar with any searching study of the amount of irradiation necessary, the exact time sequences for development of telangiectases, or the reactivity or susceptibility of the skin in different parts of the body or in different persons. Lewis, among others, discussed the great variability of these telangiectases and tested their reactivity to adrenalin and histamine, but his organizing mind never came to grips with the essence of the problem. It does not seem to have excited the attention of any perceptive radiologist to make systematic studies and so has gone by default.[3] This note describes observations I made of a woman who developed radiation telangiectases which were especially numerous and large in the periumbilical region and in a scar. I am not aware that such observations have been made previously.

Report of Case

I saw the patient for the first time in September, 1949, when she was 51 years old. She had had a strange illness which had been smoldering for approximately three years. Then a mass was felt in the abdomen. Surgical exploration in November, 1946, revealed a retroperitoneal tumor which proved to be a giant follicular lymphoma. After this she had irradiation over the abdomen: 960 r in January and 960 in April, 1947, and 1,800 in a course completed in September, 1948. She improved after the first and second sessions. There was little improvement after the third. X-rays of the alimentary canal revealed a mass outside the stomach but adherent to the greater curvature. The stomach emptied slowly.

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On examination the woman looked chronically ill. The skin in the irradiated areas was pigmented. A lymph node 3 cm. in diameter was felt below the left inguinal ligament. The abdominal wall felt somewhat thickened beneath a very thin layer of fat. The right lobe of the liver was slightly enlarged and a little tender. In the left upper quadrant there was a mass which descended on inspiration. It was tender. Pelvic and rectal examinations were negative. An operation at the age of 22 for "female trouble" left a well-healed midline scar, and in the left upper quadrant was the scar from the operation done in 1946. The rest of the findings had no bearing on her difficulty.

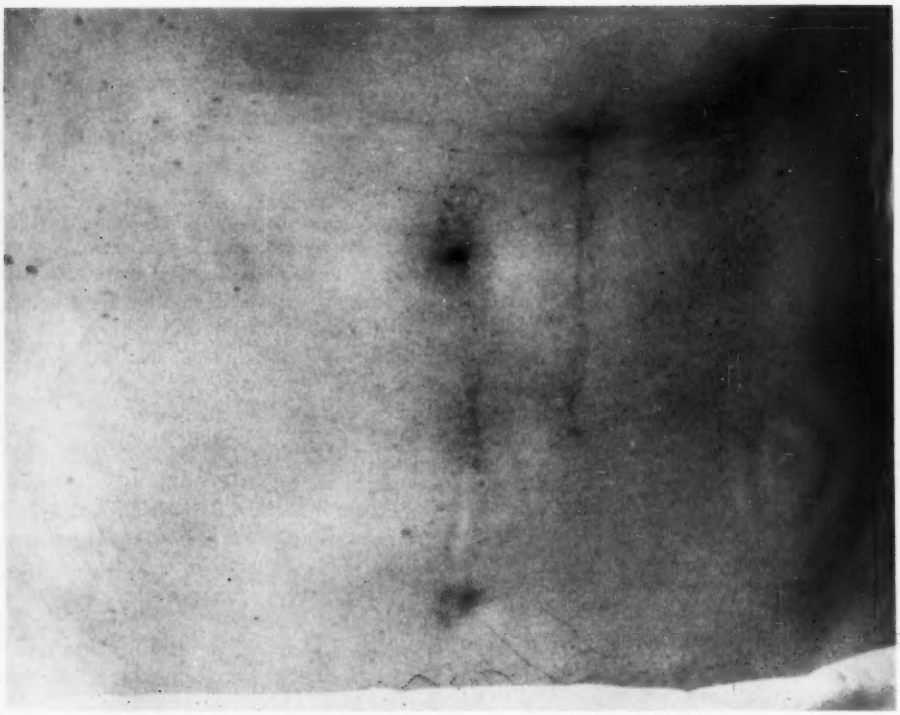
She was given 5.2 mg. of mechlorethamine hydrochloride (nitrogen mustard) on four consecutive evenings. She was sent home improved. She returned in May, 1950, and after getting 5 mg. of triethylene melamine on two consecutive days she felt much better.

She returned in September, 1952. In the interim she had suffered from an evil-smelling discharge from the umbilicus on two occasions. The hemoglobin at this time was 10.5 gm., the red cell count 3,340,000, and the white cell count 5,000, with a normal differential. She was given four more injections of mechlorethamine hydrochloride. For the first time irradiation telangiectases were seen over the lower abdomen, but I made no explicit note of any localization in the scar.

She was seen again in the office on Nov. 11, 1958. In the spring of 1958, her family physician had not been able to feel the mass, but when I saw her the mass was there. Though she still had some abdominal discomfort, her general condition was remarkable for the fact that she was so well. The urine was normal; the hemoglobin, 11.5 gm., and white cell count, 7,550. The appearance of the abdomen is shown in the Figure.

Comment

Localization of lesions in the skin has had little systematic study. The science of dermatology has not come round to solving the question. Arterial spiders, which tend to be concentrated in the upper exposed parts of the body, illustrate a peculiar regional variation in the pattern of distribution of



Photograph of the abdomen, revealing the two scars. In the older (1920), midline, scar telangiectases occur only in the part heavily x-rayed. There is no increase in telangiectases in the scar of the more recent operation (1946). Telangiectases not seen in the photograph were scattered over the left side of the abdomen from a line 3 cm. above the umbilicus to the flank, and a few were seen as far as 3 cm. to the right of the umbilicus. The margins between affected and normal skin were sharply defined.

vascular lesions of the skin.[1] Uneven distribution must be explained by variations in the extent of local susceptibility when an evenly circulated humoral force is responsible for the lesion. If direct exposure of an area of skin to an external force produces different effects in contiguous portions of the skin, local differences in susceptibility must exist. Much of the relatively little which is known about radiation telangiectasis comes from investigations of Sir Thomas Lewis,[2,3] who made some observations about them in connection with another study. He noted that they might appear as late as seven years after irradiation, and did not effect skin temperature. The large tortuous and bulbous vessels did not react normally to the local instillation of histamine or epinephrine. Thus injury had in some way rendered the vessels irresponsive as well as grossly deformed and distorted. The anemic halo around some of the telangiectatic areas he considered to be caused by a reduction in the blood flow and volume. It might be found in the skin wherever there was a region with selectively enhanced circulation. It resembles the anemic halo of the vascular spider, but it is uncertain whether the same process determines the occurrence of the anemic halo in cherry angioma.[1]

Periumbilical localization of angiomas is a feature of Fabry's syndrome, where the navel target area is more heavily peppered with the spots than neighboring regions away from the navel.[1] In our patient the skin near the navel which was most heavily marked with telangiectases got exactly the same exposure of x-rays as the skin 2-4 cm.

away, where no visible vascular lesions developed (Figure). Since there is no evidence that variations in thickness of the skin influences this distribution, we must conclude that we have an example of increased sensitivity to the effects of irradiation in the blood vessels in this region.

Scars in the skin react in varying degree to drugs or mechanical stimuli. As a general rule vascular reactivity, the triple response and other alterations are reduced.[2] Telangiectases in the abdominal scar ended abruptly at the edge of the line of exposure near the midpoint of the scar. The adjacent nonscarred skin was affected little or not at all (Figure).

This patient, who lived for an unusually long time after an operation and irradiation, illustrates two different kinds of distribution and localization of acquired vascular lesions of the skin. The exact anatomical substrate of these two kinds of localization is unknown. One probably is inherent. The blood vessels of the periumbilical skin may differ from those of adjoining skin. The vessels may be more susceptible to injury. Some other force may operate. The scar, relatively avascular, may have a low threshold for irradiation injury.

Conclusion

Irradiation over the abdomen produced telangiectases which were concentrated about the navel and were restricted to the part of a 26-year-old scar which was irradiated and did not occur in the neighboring parts of the abdominal skin. A scar which was a few months up to two years old, which got the same irradiation, was not selectively damaged in the same way. Systematic study of such telangiectases might shed light on the whole problem of vascular lesions and the patterns of their cutaneous localization. The role of the circulation in susceptibility to cancer might also be illuminated.

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Subacute Bacterial Endocarditis Treated with Oral Penicillin

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That phenoxymethyl penicillin (penicillin V) could be successfully employed in the treatment of subacute bacterial endocarditis was first demonstrated by Quinn and his associates, in 1956.[1,2] Some of their patients were treated with phenoxymethyl penicillin alone and some with this antibiotic in conjunction with intramuscular streptomycin. The following year Walker and Hamburger [3] reported four cases of subacute bacterial endocarditis caused by penicillin-sensitive streptococci successfully treated with two weeks therapy of oral phenoxymethyl penicillin and intramuscular streptomycin. As far as we know, however, no cases of Streptococcus faecalis endocarditis treated with oral penicillin have yet been reported. According to Hunter,[4] the acceptable form of therapy of S. faecalis endocarditis is a combination of 10,000,000 to 15,000,000 units of penicillin G per day, plus streptomycin. The first patient presented here was given only 1,000,000 to 2,000,000 units of penicillin per day parenterally, with the major portion of the penicillin given as phenoxymethyl penicillin. For this reason, and because our patient is one of the oldest patients (if not the oldest) with this disease on record, we wish to report our experience with the successful treatment of a 95-year-old man managed in this way. In order to provide further documentation of the feasibility of treating endocarditis with oral penicillin, this paper will include another patient successfully treated for subacute bacterial endocarditis caused by a penicillin-sensitive viridans Streptococcus.

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From the Department of Internal Medicine, The Jewish Hospital and Medical Center.

Report of Cases

CASE 1.—A 95-year-old, white, retired executive, was admitted to The Jewish Hospital on Aug. 22, 1957, because of progressive fatigability and low-grade fever of four months' duration. Although he was known to have bladder carcinoma (discovered one year previously), he was able to perform his customary activities until four months prior to admission. At that time, he developed a low-grade fever and chilliness but no actual chills. The day prior to admission the patient experienced a shaking chill, followed by a rise in temperature to 102 F. He had had a loud, systolic, apical murmur for many years, attributed to arteriosclerotic heart disease.

At the time of admission the patient was well developed and well nourished. The temperature was 101 F; the pulse was 72 per minute and regular; the respirations were 26 per minute, and the blood pressure was 140/50. There was pallor of the skin and mucous membranes, as well as generalized petechial and splinter hemorrhages. Moist rales were present at the right lung base. There was a loud, Grade 3, systolic, apical murmur which was best heard at the fourth left intercostal space near the sternum. The liver was not palpable, but the spleen was easily felt 3 fingerbreadths below the costal margin. The hemoglobin was 9.4 gm. %; the white blood cell count was 5,600. There were no significant electrocardiographic findings. Six blood cultures drawn soon after admission were positive for S. faecalis. This organism was inhibited in a twofold serial dilution test by 6.25μg. of penicillin per milliliter, 7.8μg. of tetracycline, 6.25μg. of chloramphenicol, 15.6μg. of erythromycin, 15μg. of novobiocin, and 3.9μg. of streptomycin. A portable x-ray of the chest demonstrated cardiac enlargement and pulmonary congestion.

The patient did not tolerate intramuscular penicillin well. In order, therefore, to reduce the number of intramuscular injections per day, all but 2,000,000 units of the penicillin were given in the form of oral phenoxymethyl penicillin. The patient's course is charted in the Figure. During the first week of his course he was given 400,000 units of penicillin G and 500 mg. of phenoxymethyl penicillin intramuscularly every four hours.

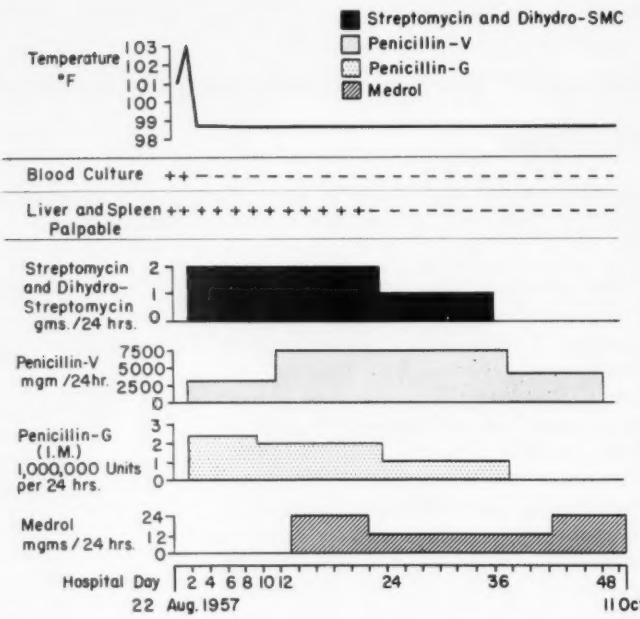

Chart for 95-year-old white man.

After one week the dosage of penicillin G was changed to 1,000,000 units every 12 hours and the phenoxymethyl penicillin was increased to 1,250 mg. every 4 hours. The schedule of treatment also included streptomycin (dihydrostreptomycin) 1 gm. intramuscularly every 12 hours. In the third week the dose of streptomycin and intramuscular penicillin G was decreased. These drugs were discontinued in the fifth week. However, phenoxymethyl penicillin was continued for two additional weeks. The patient gave a vague history of having developed urticaria in the past following intramuscular injection of penicillin G. Within two days of the institution of his present chemotherapy, a pruritic generalized macular eruption appeared. This was controlled by the oral administration of methylprednisolone (Medrol), 4 mg. very six hours. On this regimen the patient improved promptly. He became afebrile, and no positive blood cultures were recovered after the second day of treatment. By the 21st day of treatment his appetite was good; there were no petechiae; the liver and spleen were no longer palpable, and the urticaria remained under control. Fourteen months later he was still well and asymptomatic.

Like many elderly persons, he frequently used enemas and rectal instillations. Factitial lesions had developed about the anus, and it is suspected that this was the source of his S. faecalis infection.

Case 2.—A 25-year-old, white, truck driver was admitted to The Jewish Hospital on Aug. 17, 1957, with complaints of fatigability, weight loss and night sweats of four months' duration. Two weeks prior to the appearance of these symptoms, 13 abscessed teeth were extracted, but no antibiotics were given. Following this episode he developed fatigability and migratory joint pains, which began in the ankles and knees and lasted for one or two days before affecting other joints. He continued working in spite of night sweats, afternoon fever, anorexia, and a weight loss of 30 lb. He gave no history of chills, shortness of breath, or chest pain. His temperature had not been taken until he saw his physician the day of admission to the hospital.

The patient was known to have congenital heart disease with an interventricular septal defect, an enlarged heart, and a systolic murmur. He gave no past history of physical incapacitation or of heart failure. Physical examination on the day of hospitalization disclosed that the patient was well developed but showed evidence of recent weight loss. The temperature was 102 F; the pulse rate was 120 per minute and regular; the respirations were 24 per minute; the blood pressure was 160/80. The following pertinent physical findings were present: pallor of the skin and mucous membranes; one petechial hemorrhage of the conjunctiva of the right lower eyelid; a Grade 4 systolic murmur, best heard in the fourth intercostal space near the sternum, radiating to the left axilla and accompanied by a systolic thrill; palpable liver and spleen.

The admission hemoglobin was 9.7 gm. %; the white blood cell count was 7,600. Urinalysis revealed an occasional red blood cell. Six blood cultures were obtained by the day following admission. All were positive for viridans Streptococcus. The inhibiting concentration of penicillin for this Streptococcus was less than 0.025μg. per milliliter and that of streptomycin 1.2μg. per milliliter. X-ray examination showed borderline cardiac enlargement and slight dilatation of the aorta. Although the picture was not diagnostic of any particular type of heart disease, it was consistent with the clinical diagnosis of interventricular septal defect.

Treatment with phenoxymethyl penicillin * was begun the day following admission. The dosage was 1,500 mg., given at intervals of four hours for a total of 42 days. The day following admission, a questionable diastolic murmur was heard at the base, and by the eighth day this was fully developed, very loud, and of long duration; otherwise, he showed rapid improvement. The patient's appetite improved, and he was afebrile by the third day of treatment. In spite of this dramatic clinical result, the Streptococcus was reported to be relatively resistant to penicillin when tested by the disk method; however, when tested by the serial dilution technique, the minimal inhibiting concentration was found to be 0.02μg. per milliliter. Four hours after an oral dose, the penicillin blood level was 20 times as great as the minimal inhibiting concentration of penicillin for this organism.

All petechial hemorrhages disappeared by the 12th day, including those that developed after the patient was admitted to the hospital. The liver and spleen diminished in size; the hemoglobin rose steadily. On the 28th hospital day the remaining carious teeth were removed. For economic reasons the patient was discharged from the hospital on the 30th hospital day, but treatment was continued at home for a total of 42 days. At the time of discharge, he was afebrile, his appetite was good, he had regained 10 lb. in weight, there were no petechiae, and the liver and spleen were no longer palpable. However, cardiac murmurs—including the aortic diastolic murmur—persisted. The penicillin had caused no gastrointestinal symptoms at any time. He developed a tender localized area over the left wrist, which was probably an embolic episode but never proved. The tender area persisted for about one week, eventually disappeared, and did not recur. He returned to his former occupation soon after discharge from the hospital, and when last seen (14 months later) he was still asymptomatic.

* The phenoxymethyl penicillin used for this patient was supplied by Eli Lilly and Company.

Summary

Two patients with bacterial endocarditis have been treated successfully with either oral penicillin alone or with oral penicillin in combination with parenteral penicillin and streptomycin. It is particularly noteworthy that one of the patients was 95 years of age, believed to be the oldest patient on record treated for this disease.

Doctors Building (2).

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Idiopathic Paroxysmal Myoglobinuria

Report of a Case with Studies on Serum Haptoglobin Levels

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Myoglobinuria in man may follow muscle injury by direct mechanical trauma and ischemia due to vascular occlusion. Seven reports have appeared of the syndrome associated with muscular dystrophies, and it may appear in epidemic form as "Haff disease."[1,2] There are, however, cases of myoglobinuria that cannot be attributed to any known underlying disorder. Twenty-one such cases, designated "idiopathic paroxysmal myoglobinuria," have appeared in the literature; the last was reported in 1957.[3] There are, undoubtedly, many additional cases that are either not recognized, or not reported. The general aspects of myoglobinuria have been the subject of extensive reviews by Spaet, Rosenthal, and Dameshek[4]; Reiner et al.[5]; Biorck,[6] and others.

In a recent in vitro study by Javid, Fischer, and Spaet,[7] comparing the binding of hemoglobin and of myoglobin in plasma, it was demonstrated that myoglobin is not bound by the serum mucoprotein, haptoglobin. Extensive studies by several groups have established the affinity of haptoglobin for hemoglobin and its role in the renal handling of the pigment. The present paper will present a previously unreported case of idiopathic paroxysmal myoglobinuria and discuss the serum level and urinary excretion of myoglobin, and the serum haptoglobin level and its physiologic and diagnostic implications.

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Report of Case

An 18-year-old college student entered the hospital on Aug. 8, 1958, with the acute onset of muscle pain and weakness, associated with passage of dark urine. Similar episodes in 1955 and 1956 had, in each case, followed severe exertion (tennis) and subsided spontaneously after 24 hours. After the first episode, a diagnosis of acute glomerulonephritis had been entertained, but subsequent urine examinations had been normal. During the week prior to the present episode the patient had begun a program of graduated weight lifting. One day before symptoms began he had played tackle football for three hours. He noted mild generalized muscular aches on the morning of admission but despite this took part in two hours of close order marching drill. By this time severe crampy pains were present, particularly in the calves, medial thighs, and low back, and were of such severity as to produce a feeling of paralysis. Urine voided immediately after exercise was darker than usual; four hours later mahogany-colored urine was passed. One of us (A. R. S.) was called, and a blood sample was taken immediately. The patient had been in excellent health, frequently engaging in competitive athletics to the point of fatigue, without precipitating bouts of pigmenturia. There is no family history to suggest similar episodes, other muscular diseases, or endocrinopathies. At the time of admission, paralysis had cleared and examination revealed a normal-appearing, muscular youth. The only abnormal finding was spasm and tenderness of the calves, thigh adductors and flexors, and paraspinal muscles.

The initial urine specimen was dark brown, with a colorless sediment after centrifugation. The supernatant gave a strongly positive benzidine reaction and a 1+ protein test but was otherwise unremarkable. The sediment contained a few white blood cells and an occasional granular cast per high-power field. The pigment, which was identified as myoglobin by spectrophotometry and starch-gel electrophoresis, cleared gradually over 24 hours, as did the proteinuria. The plasma from the blood specimen obtained at the height of pigmenturia was not visibly discolored. A complete hemogram was unremarkable. Sternal marrow aspirate was hyper-

cellular, with increased percentage of eosinophils, plasma cells, and lymphocytes, representing nonspecific reactive changes. Serum electrolytes, fasting blood sugar, and urea nitrogen were normal. Serum glutamic oxalacetic transaminase was 1,280 units 36 hours after the onset of symptoms. An intravenous urogram and x-rays of the abdomen and chest were unremarkable.

The patient was kept at bed rest, and his urine maintained alkaline by oral sodium bicarbonate. Muscle soreness and tenderness cleared more slowly than did the pigmenturia. A biopsy specimen of the left quadriceps femoris, taken 48 hours after the onset of symptoms, showed only normal muscle. The patient was discharged with instructions to avoid fatiguing exertion.

Materials and Methods

Normal hemoglobin (AA) was prepared from lysed washed red cells of a healthy Caucasian donor. Urine and serum samples were obtained from the patient four hours after the onset of symptoms. The absorption spectrum of the urinary pigment was ascertained by analysis in a Beckman DU Spectrophotometer. Concentrations of hemoglobin (Hgb.) and myoglobin (Mb.) solutions were determined by the cyanmethemoglobin method in a Coleman Junior Spectrophotometer at 540 mμ. Plasma Mb. levels were determined by the method of Crosby and Furth.[8]

Details of reagent preparation and experimental procedures have been described fully in a previous communication.[7] Samples of serum alone, of sera containing 40, 80, 120, and 320 mg. % of Hgb., of serum containing 200 mg. % of the urinary Mb., and of urine alone were subjected to starch-gel electrophoresis at five volts per centimeter for 10 hours. The strips were cut into identical halves; one half was stained with naphthalene black (B200) and the other was stained with benzidine.

Results

The spectrophotometric curve of urine showed peaks at 546 and 586 mμ, as compared to the Hgb. peaks at 544 and 580 mμ (Fig. 1). On standing at room temperature for six hours, the dark red urine became distinctly greenish and showed a curve with maxima at 500 and 640 mμ, whereas the control Hgb. showed no change under similar conditions. The concentration of Mb. in urine was 600 mg. %; that in the serum was 40 mg. %.

On starch-gel electrophoresis the serum showed a genetically homozygous haptoglobin 2-2 pattern,[9] with no benzidine-staining bands in the region of the haptoglobin (Hp.) bands, but on addition of Hgb. the Hp.-Hgb. bands were distinctly seen and gave a positive benzidine reaction. The serum-Hgb. mixtures did not show the band of free Hgb. except at concentrations of Hgb. greater than 120 mg. %. The urinary pigment traveled with the mobility of normal human Mb., as previously described,[7] and the addition of serum had no effect on its mobility. The serum-urine mixture showed no evidence of benzidine staining in the region of the Hp. bands. These results are illustrated in Figure 2.

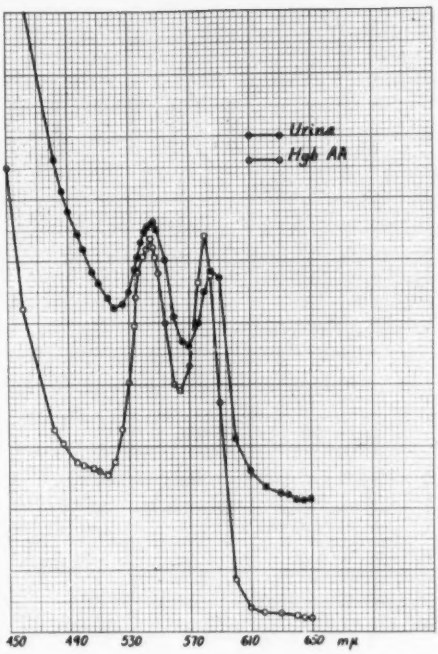

Fig. 1.—Spectrophotometric curves of Hgb. AA and of patient's urine. The urinary pigment has minima and maxima slightly to the right of corresponding ones for Hgb. (See text for detailed explanation.)

Comment

The diagnosis of myoglobinuria can often be strongly suspected from the clinical picture of acute muscle pain, weakness, and tenderness, associated with the passage of

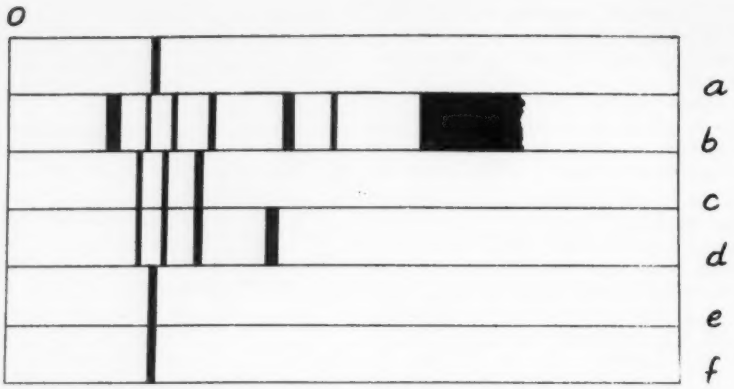

Fig. 2.—Starch-gel electrophoretic patterns of patient's serum containing Hgb. and Mb. Specimens were inserted at 0. Only the anodic segment of the strips is shown. Strip *b* was stained with naphthalene black and all others with benzidine. (*a*) Patient's serum. A faint band of Mb. has taken the benzidine stain. (*b*) Patient's serum. The bands are, from left to right: Slow α_2-band, three "$\alpha\beta$-" (Hp.), β-, fast α_2-, and the broad band of albumin. The concentration of Mb. was too low to allow staining with naphthalene black. (*c*) Serum containing 120 mg. % Hgb. The Hp.-Hgb. bands have taken the benzidine stain and show slower mobilities than the corresponding free Hp. bands in *b*. No band of free Hgb. is evident. In this and the following strip the Mb. was diluted by the added Hgb. solution and did not stain with benzidine. (*d*) Serum containing 320 mg. % Hgb. In addition to the Hp.-Hgb. bands, the band of free Hgb. is also visible. (*e*) Patient's urine. Benzidine positive band with the mobility of normal Mb. is seen. (*f*) Patient's serum mixed with his urine. The Mb. band has retained its mobility; no other benzidine-positive bands are seen.

dark urine and the absence of hemolytic disorder. Unequivocal diagnosis, however, depends upon the identification of Mb. in the urine. Since Mb. and Hgb. are the only two pigments occurring in the urine that can give a positive benzidine reaction, it remains then to differentiate Mb. from Hgb. to achieve this end. One method takes advantage of the differential solubility of the two pigments in ammonium sulfate solutions. If the urine is brought to 80% saturation by addition of 2.8 gm. of dry ammonium sulfate to 5 cc. fresh urine, virtually all the Hgb. is precipitated, leaving the supernate colorless. Mb. in urine similarly treated remains in solution.[10] Fresh urine must be used, however, since Mb. is readily oxidized to metmyoglobin on standing. The latter precipitates in 80% ammonium sulfate, leaving a colorless supernate, and therefore cannot be distinguished from Hgb. by this method. More rigorous differentiation is possible between the two pigments. Mb. may be distinguished by its electrophoretic mobility, which is slower than that of Hgb. on paper[11,12] and on starch gel.[7] Spectrophotometric analysis of the two pigments yields curves which are similar but distinguishable in a suitable instrument. The electrophoresis technique has the advantage of retaining its usefulness even if the pigments are changed into their respective met- types.

The urinary pigment in this patient had the electrophoretic mobility of normal Mb., and its absorption curve showed maxima and minima to the right of corresponding ones for Hgb., typical of Mb. The Hgb. peaks were slightly different from the standard values 540-542 and 576-578 mμ,[13] but this is due to the difference in instrument calibration, and the shift to the right of the peaks of the urinary pigment relative to those of Hgb. remains the important feature. The rapid transformation of the pigment at room temperature to the green pigment with the characteristic peaks of metmyoglobin also serves to distinguish it from Hgb., since Hgb. is known to oxidize much more slowly than Mb.[14]

A finding typical of myoglobinuria is the low plasma Mb. levels throughout the course of the disease, as compared with the high plasma Hgb. concentrations in cases of hemoglobinuria at the time when there is active Hgb. excretion. Manwell and Whipple [15] and others [16,17] ascribed this to a high "renal threshold" for Hgb. (about 130 mg. %), as compared to the low threshold for Mb. (about 17 mg. %). As Allison and Rees [18] pointed out, the concept of "renal threshold" for Hgb. falls short of accounting for certain recorded data, but no better explanation was offered until 1957 when the role of haptoglobin (Hp.) in the binding of Hgb. gradually became clear. Hp. is an α_2-mucoprotein of normal adult serum, characterized by a strong affinity for Hgb.[19] Normally there is enough Hp. in 100 cc. of serum to bind about 120 mg. of Hgb. Laurell and Nyman [20] pointed out that the Hp.-Hgb. complex (molecular weight 310,000) is too large to pass the glomerular filter. They showed that when Hgb. is injected intravenously into dogs no free Hgb. appears in the plasma or in the urine until all the Hp. is saturated. In concentrations over this, Hgb. remains unbound and is therefore presented to the glomeruli in the free form. It is then filtered and is excreted in the urine, except for the small amount reabsorbed by the tubules. Allison and Rees [18] reported absent or low Hp. levels in a number of patients with various hemoglobinurias. It was proposed independently by both these groups that the "renal threshold" for Hgb., as postulated previously, is merely a reflection of the binding of Hgb. by Hp. Allison and Rees further suggested that in patients with hemoglobinuria "the susceptibility of these subjects to hemoglobinuria is related to the low level or absence of haptoglobin in the plasma." Probably the low levels in these subjects are related to the rapid extravascular removal of the Hp.-Hgb. complex once it is formed, since many of these patients had evidence of recent hemolysis at the time their Hp. levels were determined. The removal of the Hp.-Hgb. complex is reported to proceed at a rate of 13 mg/100 cc. per hour, and Hp. regeneration is complete in about a week, provided there is no further hemolysis.[20]

In a recent in vitro study from this laboratory,[7] it was shown that there was no measurable binding of Mb. by Hp. We proposed that this explains the low renal threshold for Mb., as measured by Yuile and Clark.[21] This view is clearly confirmed by the results of the present in vivo study. The data presented establish several points:

(a) Mb. was not bound to Hp. The patient's serum was obtained when the serum Mb. level was 40 mg. % and the pigment was being rapidly excreted. On starch-gel electrophoresis this serum showed Hp. bands which stained with naphthalene black but not with benzidine (Fig. 2*a*, *b*), implying that the Mb. in the serum was not bound to the Hp. When additional Mb. from the urine was added to the serum there was still no evidence of its binding with Hp.

(b) During the episode of myoglobinuria the serum Hp. was normal qualitatively and quantitatively. This was shown by the serum Hgb.-binding capacity of 120 mg. %, well within the normal range. Thus the electrophoretic band of free Hgb. did not appear in the serum-Hgb. mixtures until the concentration of Hgb. was above 120 mg. % (Fig. 2*c*, *d*).

(c) Mb. was not bound by Hp. or any other serum protein. The mobility of Mb. was unchanged when it was mixed with serum (Fig. 2*e*, *f*). If Mb. were bound by a serum protein fraction, its mobility should have been altered.

Accordingly, it can be postulated that Mb. released into plasma remains unbound and is presented to the glomeruli in the free form. Since Mb. has a fairly small molecular size (molecular weight approximately 17,000), it is rapidly filtered and never attains high plasma concentrations. The renal threshold of 15-17 mg. %, then, more likely represents tubular reabsorption and is to be distinguished from the renal "threshold" of Hgb., which represents pre-

dominantly the affinity of Hp. for the pigment.

If a patient is seen within two to three days after an episode of pigmenturia, the differentiation between hemoglobinuria and myoglobinuria cannot be made by conventional methods unless the urinary pigment is still available for analysis. We propose the estimation of serum Hp. level as a diagnostic tool in such a case. Low or absent Hp. levels have already been reported in cases of hemoglobinuria [18]; this is because of the rapid removal of the Hp.-Hgb. complex followed by slow Hp. regeneration, as previously mentioned. The finding of a low Hp. level shortly after an episode of pigmenturia would be almost diagnostic of hemoglobinuria, whereas the finding of normal Hp. levels within three days would strongly suggest myoglobinuria or the excretion of a nonheme pigment.

Summary

A previously unpublished case of idiopathic paroxysmal myoglobinuria is reported.

Studies on the serum haptoglobin level during active myoglobin excretion are presented.

The significance of observations in explaining the "low renal threshold" of myoglobin, as contrasted with that of hemoglobin, is discussed.

The estimation of serum haptoglobin levels is proposed as a test differentiating myoglobinuria from hemoglobinuria, and its unique value in selected cases is emphasized.

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Pleurisy with Effusion in Rheumatoid Arthritis

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For almost 100 years pleurisy has been considered clinically to be one of the systemic manifestations of rheumatoid arthritis.[13,18,22,29] Although this impression was supported by postmortem evidence,[2,3,12,14] it was not until the recent development of the technique of pleural biopsy that the diagnosis was confirmed during life.[7,17]

The incidence of rheumatoid pleuritis and pleural effusion is difficult to estimate from the reports in the literature because of the difficulty of confirming this diagnosis prior to the development of the pleural biopsy technique. McCrae,[22] in 1915, reported 7 cases of acute pleurisy (one had tuberculosis) in 319 patients with rheumatoid arthritis, an incidence of approximately 2%. In a group of 510 rheumatoid arthritic patients studied by Lewis-Faning,[18] approximately 2% were found to have had pleurisy. There were 5 patients with pleurisy (1 accompanied by an effusion) in the 293 patients with rheumatoid arthritis recently reported by Short, Bauer, and Reynolds.[29] In two of the patients pleurisy was associated with tuberculosis or bronchiectasis, but in the remaining three pleurisy presumably constituted a systemic manifestation of rheumatoid arthritis. In their series there were nine additional patients and five controls who gave a history of one or more attacks of pleurisy.

Few postmortem examinations of patients with rheumatoid arthritis have been performed, but in the autopsied cases pleurisy, pleural adhesions, and pleural effusions have been described rather frequently.[2,4,6,9,12,14,23,24] In the largest postmortem series reported,[2] fibrous pleural adhesions were found in 73% of the patients. There have been several interesting cases studied post mortem in which nodules typical of rheumatic fever[3] and rheumatoid arthritis[4,6,16] have been found in the pleura, and in three of the latter cases pleural effusion was also present. In an additional case,[24] lesions resembling, but not typical of, rheumatoid nodules were found in the pleura associated with a pleural effusion.

Although there have been a number of reports * on the pulmonary manifestations of rheumatoid arthritis since Ellman[8,9] revived interest in this subject 10 years ago, there have been only a few cases in which pleural effusion was a prominent feature.[4,6-11,17] To date we have been able to obtain from the literature a total of only 19 cases in which a pleural effusion was present and

* References 4-11, 15, 16, 19-21, 23, 24, 26-28.

Pleural Effusion Associated with Rheumatoid Arthritis

Author	Age	Sex	Duration of Arthritis	Autopsy or Biopsy	Steroids
Bevans	52	F	10+ yr.	Yes (A)	Yes
Bevans	46	F	15 yr.	Yes (A)	Yes
Christie	57	M	12 yr.	Yes (A)	?
Christie	67	M	6 wk.	Yes (A)	No
Christie	53	F	30 yr.	Yes (A)	No
Douglass	--	--	--	Yes (B)	--
Ellman	48	F	9 mo.	Yes (A)	No
Ellman	63	M	--	No	Yes
Ellman	58	F	6 yr.	No	--
Emerson	50	M	10 yr.	No	--
Emerson	45	F	7 yr.	No	--
Emerson	45	M	3 mo.	No	--
Emerson	48	F	2 yr.	No	--
Emerson	54	M	2 yr.	No	--
Emerson	50	M	3 wk.	No	--
Gruenwald	55	M	6 yr.	Yes (A)	No
Heller	56	M	2 mo.	Yes (B)	--
Raven	62	F	30 yr.	Yes (A)	No
Short	--	F	--	--	--
Lee	57	M	6 yr.	Yes (B)	Yes
Lee	65	F	12 yr.	No	Yes

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appeared to represent a systemic manifestation of an existing rheumatoid arthritis (Table). In eight of the cases the diagnosis was confirmed post mortem,[4,6,9,14] and in two, by pleural biopsy.[7,17] In only one of the latter two cases, however, was the biopsy specimen typical of a rheumatoid lesion.

The present report concerns two patients with rheumatoid arthritis who have had large pleural effusions which we believe represent systemic manifestations of rheumatoid arthritis. In one of our cases diagnosis was confirmed by thoracotomy and pleural biopsy. Additional points of interest in these two cases include the presence of rheumatoid factor in high titer (F-II agglutination titers in excess of 1:56,000†), the absence of L. E. cells in the peripheral blood and distinct clinical improvement coincident with chloroquine therapy.

Report of Cases

CASE 1.—A 57-year-old agricultural inspector who has been followed at the Palo Alto Medical Clinic since 1939, when he was examined because of indigestion, first developed rheumatoid arthritis in 1948. The onset was insidious with arthralgia, and when the patient was examined thoroughly in 1949 he had joints which appeared to be normal. Between 1948 and 1950 he had several flare-ups of his arthritis, associated with prostatitis and dental infection. Therapy with penicillin plus appropriate local therapy on each occasion cleared the infection, and with this the arthritis markedly improved. Repair of an inguinal hernia in 1950 was followed by a generalized flare-up of his arthritis which did not respond to rest and salicylates. Cortisone was administered in late 1950 and early 1951 with gradual improvement, and he returned to full-time work in June, 1951. He did fairly well without steroids during most of 1952 and 1953. In 1953 an arthrotomy was performed on the right ankle because of osteochondritis dissecans secondary to rheumatoid arthritis. Synovial biopsy at the time of surgery was consistent with rheumatoid arthritis. After surgery he did well and did not return for a medical check-up until February, 1955.

In February, 1955, the patient had very few complaints but was found on physical examination to have impaired resonance and a few rales at the left lung base. The joints were practically normal. Roentgenograms of the chest revealed a vague diffuse increased density in the left lateral and lower chest, interpreted at that time as thickened pleura. He got along well until October, 1955, when his arthritis again flared up, especially in the right wrist and knee. Steroid therapy was followed by a gradual remission of symptoms. Roentgenograms in April, 1956, revealed increasing density at the left base, and physical signs at that time suggested pleural fluid. Lemon-yellow fluid was aspirated on thoracentesis from the left chest. The fluid revealed only inflammatory cells, and it was negative for malignant cells. Cultures were negative for tuberculosis. Skin tests were also negative for tuberculosis, coccidioidomycosis, and histoplasmosis. It was felt at that time by the patient's personal physician (H. S.) that the pleural effusion represented a manifestation of rheumatoid arthritis. The patient was followed carefully, and he was continued on steroids because of persistently active arthritis. Serial chest roentgenograms revealed persistence of the fluid. In April, 1957, the patient was hospitalized for an arthrodesis of the right ankle and at the same time thoracentesis was performed, again revealing only inflammatory cells in the pleural exudate. No evidence of malignancy or tuberculosis was found. A synovial biopsy specimen obtained from the ankle at the time of surgery was consistent with the diagnosis of rheumatoid arthritis. Repeat chest roentgenograms were essentially unchanged in June, 1957. In December, 1957, there was a marked increase in the pleural effusion, but there was no accompanying exacerbation of arthritic symptoms. He had taken steroids only occasionally during 1957 and had been working throughout the year except for the period of hospitalization and immediately postoperatively.

The patient was readmitted to the Palo Alto hospital on April 21, 1958, with physical signs of left pleural effusion and rheumatoid nodules on both forearms. Significant laboratory tests performed during this entry included F-II agglutination titer in excess of 1:56,000, negative L. E. clot test, and no evidence of malignancy or tuberculosis on reexamination and culture of the pleural fluid.

The patient had a thoracotomy and pleural biopsy. This procedure was carried out because of a pleural mass which persisted after thoracentesis. Although this ultimately proved to be loculated fluid, a definitive preoperative diagnosis could not be established. The pleura was found to be markedly thickened, and findings on biopsy of pleura (Fig. 1) and muscle (Fig. 2) were consistent with the diagnosis of rheumatoid arth-

† Test performed through the courtesy of Dr. Wallace Epstein, University of California Medical Center, under a grant from the Northern California Chapter of the Arthritis and Rheumatism Foundation.

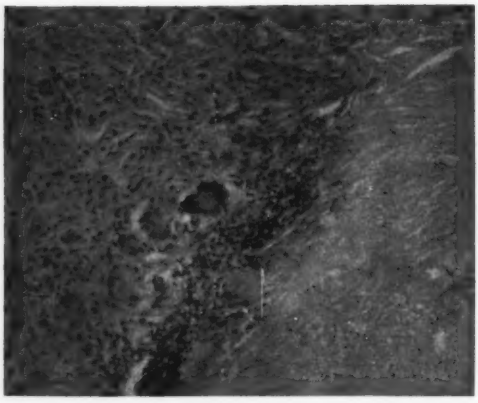

Fig. 1.—Pleural biopsy specimen from Case 1. This illustrates thickened pleura and one area of nodule formation with palisading or mononuclear cells and lymphocytic infiltration.

ritis. After surgery, the patient developed a local reaction to an intramuscular injection of penicillin given for acute bronchitis. Also, immediately postoperatively, he had a flare-up of his pleuritis, with pain and increased pleural effusion. There was not, however, any flare-up of his arthritis. The patient was treated initially with methylprednisolone and penicillin. He was given antihistamines and corticotropin (ACTH) when the urticarial reaction to penicillin developed. With this therapy there was gradual improvement. Prior to discharge from the hospital, therapy with chloroquine was also initiated. After discharge the patient continued to reaccumulate fluid in the left pleural space. He developed chills, fever, marked weakness, and fatigue. Because of this he was rehospitalized on May 15, 1958. During this hospitalization methylprednisolone was gradually discontinued and chloroquine therapy was continued. Progressive improvement in the patient's general condition, in the physical findings, and in the radiographic evidence of pleural effusion resulted. At the time of his last examination, in November, 1958, he was practically symptom free and, on percussion and auscultation of the chest, only minimal differences were noted between the right and left chest. He had no joint symptoms and no undue fatigue.

Case 2.—A 65-year-old white housewife was first examined in the internal medical section of the Palo Alto Medical Clinic on Dec. 4, 1957, because of a "positive" minifilm. The patient had developed rheumatoid arthritis, with involvement of the fingers and hands, 12 years before entry. The disease progressed relentlessly to involve the feet, knees, elbows, and hips, and it produced a slowly progressive crippling, with marked secondary hypertrophic arthritis in the knees and hips. She had prior therapy with salicylates, gold, cortisone, hydrocortisone, rest, and physical therapy. Two months prior to examination at the clinic she developed general malaise, fever, considerable nasal congestion, postnasal discharge, productive cough, and bilateral anterior chest pains. On examination, she was afebrile but had a purulent postnasal discharge, bilateral pleural effusions, and joint de-

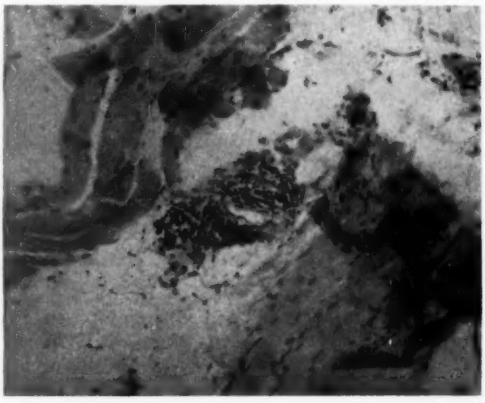

Fig. 2.—Muscle biopsy specimen from Case 1. This illustrates perivascular infiltration of lymphocytes consistent with diagnosis of rheumatoid arthritis.

formities in the hands, feet, hips, and knees, which were typical of rheumatoid arthritis associated with severe secondary hypertrophic arthritis, and she had rheumatoid nodules on both forearms. Diagnostic studies included skin tests for tuberculosis, coccidioidomycosis and histoplasmosis, examination of pleural fluid for malignant cells, culture of the pleural fluid, L. E. clot tests, F-II agglutination titer, blood serology, complete blood cell count, urinalysis, sputum smears and cultures, serum protein electrophoretic pattern, and chest roentgenograms. Positive findings included bilateral pleural effusions on the chest roentgenograms, greater on the left than the right; F-II agglutination titer in excess of 1:56,000; hemoglobin of 11.3 gm.; a sedimentation rate of 53 mm. (Wintrobe); microhematuria, pyuria, cylindruria, and albuminuria (traces to 1+), and a slightly elevated β-globulin in her serum proteins. Other studies were either negative or within normal limits, except for the pleural fluid, which revealed inflammatory cells in the exudate. After initial diagnostic studies, the patient was treated with a broad-spectrum antibiotic without any apparent change, except for a gastrointestinal upset and then the therapy was discontinued. She also had symptomatic therapy for cough and nasal congestion. After thoracentesis had been performed, therapy with chloroquine (250 mg.) was initiated and her symptomatic therapy was continued. Serial chest roentgenograms until April revealed little change in the fluid on the right and a gradual increase in the fluid in the left chest, despite gradual general clinical improvement. She improved in strength and energy; her cough decreased; gradually she was able to walk with the aid of crutches, and finally she was able to walk around her house without crutches. The most recent chest roentgenograms (late April) revealed considerable clearing of the fluid in the left pleural space and some decrease in fluid at the right base. At present, she is free of joint pain at rest and she has no cardiorespiratory symptoms.

Comment

There is no question that pleurisy and pleural effusion may represent systemic manifestations of rheumatoid arthritis. Effusion may be large or small, and it may be associated with clearly defined cardiorespiratory symptoms or it may go relatively unnoticed until postmortem examination. Pleural effusion may be associated with other manifestations of systemic involvement, such as weight loss, fever, and general malaise, but undoubtedly, in some cases, it occurs without such symptoms. In almost all cases reported to date, the joint symptoms have antedated the onset of pleural effusion by months or years.

In contrast to the usual age and sex distribution for rheumatoid arthritis, this particular manifestation has not, to our knowledge, been found in any patient under 45 years of age and it occurs with approximately equal frequency in males and females.

Although subcutaneous nodules were specifically mentioned in only a few of the cases reported to date, we noted them in both of our patients, and we wonder if the patient with subcutaneous nodules is perhaps more liable to develop pleurisy and pleural effusion than is the patient who does not have nodules.

Steroid therapy has recently been implicated as a possible factor in the increasing number of rheumatoid arthritic patients who appear to be developing severe systemic manifestations involving particularly the cardiovascular system. In the patients with pleural effusion reported to date, three, and possibly four, had steroid therapy. Steroid therapy was not mentioned specifically for the other patients, and in five cases steroid therapy either was specifically denied or the cases occurred prior to the advent of steroid therapy. Steroids had been given to both of the patients that we have studied. Whether this plays any part in the development of pleural effusion in rheumatoid arthritis we do not know, but we believe that this is unlikely.

One of the characteristic features of the pleural effusions occurring in the patients with rheumatoid arthritis reported to date, including our own, has been the persistence of the effusions for months or years. In the cases previously reported, the effusions have not clearly been influenced by rest, salicylates, steroids, diuretics, or digitalis. In our two patients, rest and salicylates appeared to have no effect, and in one steroids appeared to be without effect. In both of our patients, however, therapy with chloroquine phosphate appeared to coincide

with clinical improvement. This was particularly striking in Case 1. We hesitate to attribute the improvement in these patients to this particular therapy but, because this possibility cannot be excluded, we believe that further trial with chloroquine therapy in rheumatoid arthritis associated with pleuritis and pleural effusion is indicated.

To our knowledge, there have been no previously reported cases of pleural effusion associated with rheumatoid arthritis in which rheumatoid factor has been demonstrated. The finding of high titers of rheumatoid factor in our two cases is consistent with the experience of others who have noted high titers in patients who have subcutaneous nodules, long-standing disease, and demonstrable bone destruction on x-ray.[30]

No discussion of pleural effusion as a manifestation of rheumatoid arthritis would be complete without a word about specificity and diagnosis. Aronoff and associates[1] raised some question about the specificity of the pulmonary lesions in rheumatoid arthritis. In 253 patients with rheumatoid arthritis they found only a slightly higher incidence of pulmonary disorders than in the general population, and in none of their patients were any lesions found which they considered specific for this disease. In comparing roentgenograms of patients and controls, they noted no differences, and in 42 necropsies no specific pulmonary lesions were found. Various workers[7,11,17] have pointed out the necessity of careful diagnostic work-up in patients with pleural effusion, with or without rheumatoid arthritis. Particular consideration must be given to neoplasm, tuberculosis, systemic lupus erythematosus, and rheumatic fever. We believe that pleural biopsy either by thoracotomy or by needle is a very helpful diagnostic aid in cases of so-called "idiopathic" pleural effusion, and it should be used when any doubt exists regarding diagnosis. In one of our two cases diagnosis was confirmed by pleural biopsy, and in the other case the patient refused to permit a biopsy to be performed.

Summary and Conclusions

Two patients with rheumatoid arthritis who developed large pleural effusions as a systemic manifestation of their rheumatoid disease are reported. In one, the diagnosis was confirmed by pleural biopsy, and in the other, the clinical course was considered to be consistent with this diagnosis.

Outstanding features of the two cases included the presence of subcutaneous nodules, a high titer of rheumatoid factor in the serum, long-standing disease, joint destruction on roentgenogram, age of the patients above 55 years, and persistence of the pleural effusions.

In both patients clinical and roentgenographic improvement occurred coincident with chloroquine therapy, and we believe this coincidence warrants further trial of this drug under similar circumstances.

Pleural effusion occurring concurrently with rheumatoid arthritis may be a systemic manifestation of this disease, and, while other causes (especially neoplasm, tuberculosis, systemic lupus erythematosus, and rheumatic fever) should be sought, the effusion can be explained on the basis of rheumatoid arthritis alone.

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Mediastinal Neurofibrosarcoma Causing Hypoglycemia

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Nonpancreatic fibrogénic tumors producing hypoglycemia are very rare and have been reported in only 11 instances thus far. Several theories have been advanced in explanation of this phenomenon. Some authors thought to have seen structures in the tumor resembling islet cells [1,2]; others made the increased utilization of carbohydrates by these huge tumors responsible for the hypoglycemia.[3,4] The explanation closest to my physiologic concepts, so far, has been given by August and Hiatt, who attributed to the neoplasms the ability to secrete an agent with insulin activity.[5] This explanation, however, seems to be incomplete without the implied assumption that only neurogenic fibrosarcomas are capable of releasing agents with hormone activity or, if I may add, with hormone-activating properties.

It is, therefore, permissible to assume that most, or perhaps all, of the hitherto reported fibrogenic neoplasms associated with hypoglycemia were of nervous origin. The morphologic similarity between the two types of fibrogenic tumors makes it, at times, difficult to distinguish between an ordinary fibrosarcoma and a neurogenic fibrosarcoma.

The case presented here, however, seems to remove any doubt about the nervous origin of this tumor. This is not only suggested by the histological picture (especially the whorls) but is also assured by the observation at surgery that the tumor arose directly from a sympathetic nerve trunk with a nerve forming the root of the pedicle. The significance of these findings in the process leading to hypoglycemia is obvious. The mode of action, however, remains open to discussion.

Submitted for publication Jan. 29, 1959.

Report of Case

A 51-year-old white housewife was admitted to the Edgewater Hospital with a tentative diagnosis of cerebral thrombosis. The past history of this case revealed a variety of symptoms, mostly cerebral in type, which made further investigation obligatory. Two months prior to the admission, she started to feel sleepy, easily fatigued, and moderately depressed. These symptoms were attributed to the antihypertensive drugs the patient was taking at that time. Cessation of the Rauwolfia therapy did not bring about relief of these symptoms. On the contrary, the lassitude became extreme; she became confused at times and forgetful, with the depression increasing. She also noticed weakness of the right arm, with inability to raise it to its full extent, and simultaneous paresthesia of the right finger tips. On several occasions, she slept around the clock and could be aroused only with difficulty. Twice, in the early morning hours, she fell into a coma accompanied by general convulsions. After these two episodes, her right upper extremity was temporarily paralyzed. On the day of admission to the hospital, the relatives noticed her excessive fatigue, confusion, anxiety, slurred speech, gradually increasing paresis of the right arm, and, finally, somnolence terminating in deep coma.

Physical examination revealed a well-nourished woman in deep stupor, the face flushed and puffy, the respiration stertorous. The pupils were reacting to light; the fundi did not show choke, retinal hemorrhages, or exudates. The right upper extremity was paretic; patient did not respond to vocal commands; she was, however, responsive to painful stimuli. Babinski reflexes in both lower extremities were positive; the tendon reflexes increased. Pulse, 70 per minute regular; blood pressure, 180/100. Chest examination revealed flatness on percussion over the right posterior aspect of the thorax below the angle of the scapula, with diminished breathing sounds. The heart was markedly enlarged to the left, with the apical impulse displaced downward and outward beyond the midclavicular line. No murmurs were heard.

The abdomen did not show any abnormalities. The liver and spleen were not palpable, and there was no resistance or mass to be found.

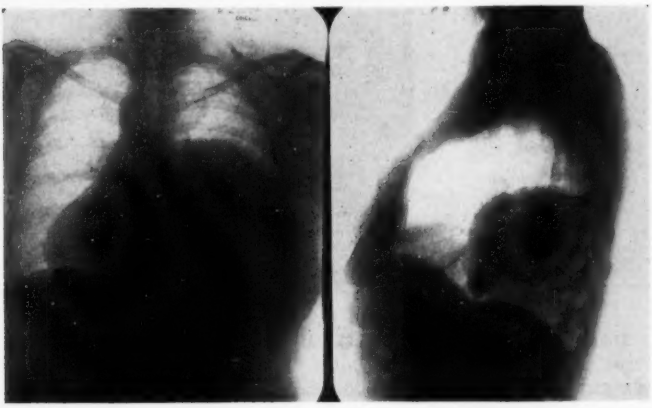


Fig. 1. — Roentgenogram of the chest.

Lumbar puncture showed pressure of 210 mm. of water. The spinal fluid was crystal clear. Pandy and colloidal gold tests were negative. Cells, 4; total protein, 40; Kahn, negative.

RBC, 4,400,000; WBC, 5,000; Hb., 13.0, 84%; HCT., 42%; VDRL, negative. Blood sugar value during seizure, 36 mg. %; otherwise, between 41 mg. % and 51 mg. %; two hours after breakfast, 132 mg. %. Urinalysis did not reveal any pathology.

Roentgenogram of the chest revealed a mass about 15 cm. in diameter in the right lower posterior lung field, which did not appear to involve the pulmonary parenchyma (Fig. 1). X-ray examination of the skull revealed no evidence of increased intracranial pressure. The sella turcica and petrous ridges were normal in appearance. There were no abnormal intracranial calcifications.

The EEG was not conclusive, since no sleep could be obtained despite secobarbital (Seconal) sedation and prolonged recording.

The patient was put on a high-carbohydrate diet with frequent feedings. Subsequent seizures occurred mostly in the early morning hours and were terminated almost immediately by intravenous administration of 50 cc. of 50% dextrose solution. The seizures were accompanied by grand mal type epileptiform convulsions with biting of the tongue and were followed by transient paresis of the right upper extremity. Coming out of the comatose stage, the patient at first was antagonistic, belligerent, and agitated, but she became cooperative and pleasant after a while. Aware of the preceding seizure, she felt embarrassed about her involuntary bed-wetting during the seizure and was deeply depressed and frightened.

It was finally decided to remove the intrathoracic tumor, hoping to eliminate with it the source of the hypoglycemia. Since there was no evidence of hepatic disease or pituitary or adrenal hypofunction, which could also account for hypoglycemia, the alternative of exploration of the pancreas was still left open in case of failure to achieve the expected result.

A right-sided thoracotomy was performed by Dr. William M. Lees. With use of continuous intravenous drip of 10% dextrose in water the chest was opened. The ribs were spread, and a huge tumor mass was found in the right hemithorax, attached by a pedicle to the area of the mediastinum immediately inferior to the azygos vein and extending posteriorly along the sympathetic nerve chain and the sixth intercostal nerve. The tumor was removed from the chest pedicle. This was then dissected free, and a nerve was found to be the root of the pedicle, which apparently arose from one of the sympathetic nerve trunks.

The extirpated specimen weighed 1,600 gm., measured 190×180×150 mm., and consisted of a lobulated encapsulated soft-tissue mass (Figs. 2 and 3). Microscopically, the sections revealed a structure composed of spindle-shaped cells with a hyperchromatic nucleus and scant cytoplasm. These cells were arranged in interlacing bundles and whorls (Fig. 4).

Fig. 2.—Tumor.

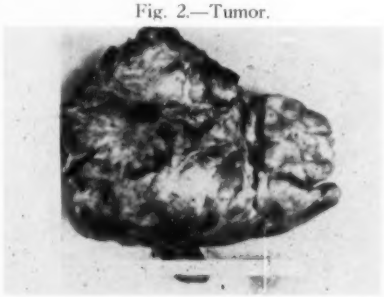


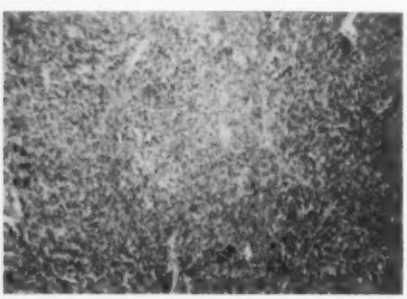
Fig. 3.—Cross section of the tumor.

Postoperatively, patient was and remained symptom free, with no hypoglycemic episodes appearing any more. Glucose-tolerance tests taken on the fifth day after surgery and repeated at regular intervals thereafter were found to be normal. X-rays of the chest, taken three and seven months after the operation, did not reveal any pulmonary or mediastinal pathology.

Summary

A case of a mediastinal neurofibrosarcoma associated with severe hypoglycemia of the fasting cerebral type is presented. Removal of this neoplasm was accompanied by complete disappearance of all the neurologic symptoms and the return of the blood sugar level to normal. It is felt that there is reason to assume that those fibrosarcomas capable of producing hypoglycemia originate from the sympathetic nervous system.

Fig. 4.—Photomicrograph of the tumor, showing whorls.



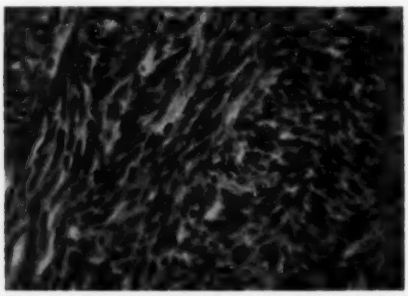


Fig. 5.—Photomicrograph of the tumor in high-power view.

1902 W. Addison St. (13).

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An Unusual Bone Lesion in an Adult with Myxedema

Report of a Case and Review of the Literature

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Recently a young man was admitted to the orthopedic service of Brooke Army Hospital with bone pain and an osteolytic lesion of the right femoral head. The opinion of the staff members and consultants was that the lesion was either infectious or neoplastic in origin. The patient's general physical appearance, however, suggested that the patient probably had an endocrine disturbance as well, and it was felt that the patient should be medically evaluated prior to any surgical procedure. All concerned were of the opinion that if any endocrinopathy was present it was certainly an incidental finding.

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From the Department of Medicine, Brooke Army Hospital, Brooke Army Medical Center, Fort Sam Houston, Texas.

Fig. 1.—X-ray of the pelvis, taken on admission, showing a large cystic area involving the lateral aspect of the right femoral head.

After extensive medical evaluation it was determined that the patient had primary myxedema, and he was started on therapy in preparation for surgery. The question as to a possible relation between myxedema and the type of bone lesion presented was discussed in detail with members of the consultant staff in the departments of medicine, orthopedics, and radiology. No one knew of any lesion of this nature associated causally with myxedema in an adult. A brief review of the literature also failed to disclose any reports of lesions of this nature in myxedema.

The patient's complete recovery following the institution of therapy with dessicated thyroid alone indicated to us that the bone lesion and myxedema were probably causally related, and, since an extensive review of the domestic and foreign literature indicated no reports of cases similar to ours, it was felt that this case should be reported, particularly in view of the conditions with which such a bone lesion might be confused.

Report of Case

History.—A 22-year-old active-duty Private in the Army, of Indian extraction, two months prior to admission developed pain in his right hip and buttock with radiation down the anterior aspect of the thigh to the knee, which was aggravated by walking. The pain became increasingly severe, and he was admitted to the orthopedic service of our hospital for further studies. There he was found to have a destructive lesion of the right femoral epiphysis (Fig. 1), which was thought to represent either a chondroblastoma or chronic inflammatory disease, such as tuberculosis. Family history reveals that the patient's mother had a thyroidectomy for a nontoxic goiter prior to his birth but is otherwise negative. The patient completed the 10th grade in school but had a moderate amount of difficulty with his studies. He was unmarried. The patient had no previous illness of note, and his system review was essentially negative. He stated that he had noted no change in his physical appearance or mental state in recent years.

Physical Examination.—This revealed a well-developed, muscular man who was cooperative but with very slow husky speech, a short attention span, and a dull monotonous vocal tone. His height was 5 ft. 7 in.; weight, 146 lb.; pulse, 72, and blood pressure, 104/90. There was a marked puffiness of the face, with sparsity of facial, axillary, and body hair (Fig. 2). The skin was rather soft, and there was no palpable enlargement of the thyroid gland. There were no herniae. Genitalia were normal. No abnormalities were found in the patient's general body build and configuration. There was general limitation of motion of the right hip, particularly on internal rotation and flexion, due to pain. There was no point tenderness and no objective findings other than the above. The neurological examination revealed no motor or sensory defect. There were no abnormal reflexes. The deep tendon reflexes demonstrated the classic pseudoclonus of myxedema.

Laboratory Data.—Complete blood cell count revealed a white cell count of 9,200, with 58% neutrophils and 42% lymphocytes. Hemoglobin was 11.5 gm. per 100 cc.; hematocrit, 34 vol. %, and sedimentation rate, 8 mm. Urinalysis was within normal limits. Serology was negative. Serum calcium was 5.3 mEq. per liter; inorganic phosphorus, 3.6 mg. %, and alkaline phosphatase, 5.0 Bodansky units. Skin tests for tuberculosis, histoplasmosis, and coccidioidomycosis were negative in all concentrations tested. Twenty-four-hour urine steroid excretion revealed 17-ketosteroids 4.06 mg. and 11-oxycorticoids 1.46 mg. Gonadotropin assay was performed which showed less than 50

Fig. 2.—Admission photograph, showing marked myxedematous facies.

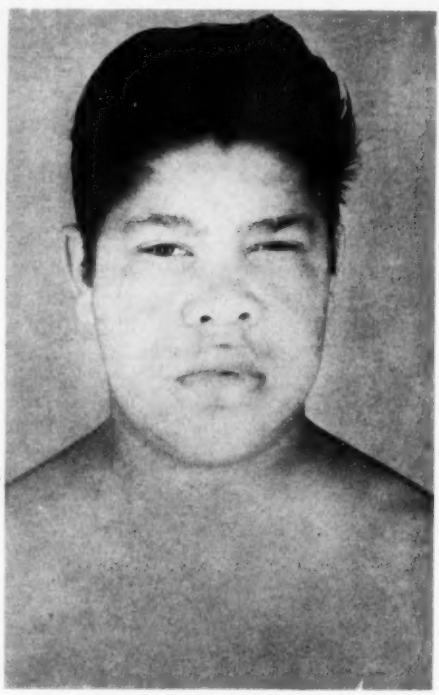

Fig. 3.—Repeat x-ray two months after treatment with thyroid extract, showing some increase in the deposition of calcium in the lesion.

M. U. per liter. A repeat 17-ketosteroid study showed a level of 9.76 mg. per 24 hours. Studies of thyroid function revealed the following: Initial protein-bound iodine was 1.3μg. %, serum cholesterol 334 mg. %. Following therapy, the protein-bound iodine rose gradually to a level of 5.2μg. % and the cholesterol fell to 140 mg. %. The initial I^{131} uptake before TSH stimulation was less than 1% in 24-48 hours. Four days after daily TSH stimulation, the I^{131} uptake was still less than 1%, which indicated primary myxedema. An initial electrocardiogram showed low voltage, delayed intraventricular conduction, and right axis deviation. Initial x-rays showed a large cystic area involving the lateral aspect of the right femoral head (Fig. 1), which had progressed slowly since April, 1957. A general bone survey showed no other abnormalities. Follow-up x-rays during therapy showed rapid improvement, as indicated in Figures 3 and 4.

Course in Hospital.—After the diagnosis of primary myxedema was established, the patient was placed at bed rest and started on 1/8 grain (8.1 mg.) of dessicated thyroid, U. S. P., daily, and this was increased slowly every five to seven days until he was taking a maximum of 3½ grains (226.5 mg.) daily. There was steady clinical and laboratory improvement, with great decrease in the puffiness of the face and body (Fig. 5), improvement in the slow speech and slow cerebration, and an increase in interest in his surroundings with an improvement in general personality. Within two months after therapy was started the patient was felt to be euthyroid, with a cholesterol of 155 mg. % and a protein-bound iodine of 5.2μg. %. His blood cell count had returned to normal.

He was then seen by the orthopedic service, where he was fitted with an ischial tuberosity brace to his right leg and was then able to ambulate without difficulty. The x-rays showed significant improvement in the lesion during thyroid replacement alone, and it was felt that, although continued improvement would be manifested, the patient should not be subjected to full field duty, and since he was agreeable to being separated from

Fig. 4.—X-ray taken 3½ months after the onset of therapy, showing striking resolution of the lytic process.

the service, he was discharged from the Army. The question of biopsy was discussed with the patient. Unfortunately, he refused the procedure.

Comment

There is general agreement that lack of thyroid hormone may result in characteristic bone changes if the deficiency occurs during the years of growth and development. This is well documented in all texts on thyroid disease as well as numerous articles in the literature.[1]

In addition to a general lag in bone age and delayed development of centers of ossification, there is a characteristic x-ray appearance which has been termed epiphyseal dysgenesis. The ossification of the epiphyseal cartilages may take the form of multiple foci which finally coalesce into an irregularly shaped center, often stippled. Under therapy, these centers rapidly assume their normal configuration, and, although any bone may be involved, the changes are most consistent and striking in the head of the femur. These changes are considered to be a disorder in growth and development of cartilage and are probably akin to the diseases classified as osteochondritis deformans juvenilis, particularly osteochondrosis of the capitular epiphysis of the head of the femur, or Legg-Perthes disease.[2] However, the treatment of these diseases with thyroid has not been shown to be of value.[3] Serum calcium phosphate and alkaline phosphatase levels are within normal limits in adult myxedema, as they were in our patient. High levels of serum calcium and subnormal levels of serum alkaline phosphatase are frequently seen in cretinism or juvenile myxedema, and these return to normal with thyroid therapy.[4]

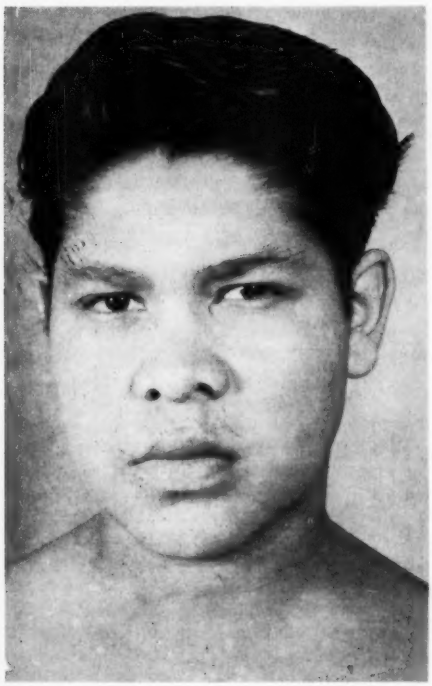

Fig. 5.—Two months after institution of therapy, with considerable improvement in appearance.

Studies have shown that thyroid deprivation may have an effect on hyaline cartilage and suggest that the metabolism of chondroitin sulfuric acid is influenced by thyroid.[5] There have been a number of attempts by orthopedists and endocrinologists to link Perthes disease and hypothyroidism,[6] but there is no real evidence for this. It is conceivable, though, that in some cases there may be a relationship. However, when hypothyroidism develops early in life, the characteristic changes of epiphyseal dysgenesis are widespread and bilateral and are not accompanied by pain or disability. The single exception appears to be Wilkins case[7] of a 7-year-old girl with hypothyroidism, who developed a painful lesion of one hip. X-rays showed flattening and fragmentation of the head of the femur. This is the only example we were able to find in the American literature that had any similarity at all to our patient.

The foreign literature is replete with material on children; however, there were virtually no reports of changes described in adults. Von Stubenrauch,[8] in 1911, described a case of a 34-year-old man suffering from myxedema, during the course of whose illness the interphalangeal joints of both big toes were completely destroyed. The process appeared to be limited, and clinically the pain seemed to be caused by the resulting deformity of the toes. His opinion was that the changes, microscopically, were identical to those seen in von Recklinghausen's osteitis fibrosa and, furthermore, that their origin might be connected with an existing malfunction of the thyroid gland. There was no discussion of therapy in this article.

In our case, of course, it is impossible to ascertain whether or not the combination of the lesion of Legg-Perthes disease and myxedema is any more than coincidental. However, the age of the patient, the fact that initially there was no response to bed rest alone, and the rapid clinical and x-ray response to thyroid medication leads us to believe that the disorder was produced, at least in part, by the lack of available thyroid hormone. Inflammatory diseases (such as tuberculosis) or neoplastic diseases (such as chondroblastoma) were considered and felt to be excluded by the negative skin tests and the fact that healing occurred with no therapy other than thyroid extract.

It is reasonable to consider whether or not our patient was actually a cretin with the onset of his disease being somewhat later in life than is usual. Unfortunately we are unable to exclude this entirely, as the onset of his illness cannot be determined accurately. However, we believe that cretinism is unlikely, owing to the fact that he was reasonably intelligent and demonstrated none of the physical stigmata usually associated with cretinism, such as the extremely short stature, abnormally protruded abdomen, sexual maldevelopment, and the above-described generalized bone changes.

Juvenile myxedema is an intermediate state between cretinism and adult myxedema.

The marked myxedematous symptoms which were found in our patient are rarely seen, and our patient did not demonstrate the infantile extremity-trunk ratio of juvenile myxedema. Again, any bony changes, as described under epiphyseal dysgenesis, are invariably generalized.

It is certainly possible that in our patient, at the time of the onset of his illness, all the epiphyseal cartilages were mature, except the one in which the lesion was produced, and that this unusual combination of circumstances occurring at just the opportune time resulted in the clinical situation as seen by us. However, this must be speculation, as we were unable to obtain a biopsy specimen. Certainly other etiological factors cannot be ruled out, such as a primary vascular defect. It is known that hypothyroidism is accompanied, along with the diminished oxygen consumption of the body, by a markedly reduced cardiac output and peripheral blood flow.[9] Stewart [10] has shown that an increased arteriovenous oxygen difference is present, implying that though the circulatory needs of the body are markedly lowered the heart does not maintain circulation adequate for these requirements. The peripheral blood flow is markedly reduced and may be reduced out of proportion to the decrease in basal metabolic rate. A further circulatory finding is a low plasma and circulating blood volume.[11]

Although there have been no studies linking the bone changes seen in cretinism or osteochondritis deformans juvenilis and decreased blood supply to the bony and cartilaginous tissues involved, this has been discussed frequently. The possible relationship is still unresolved.

Summary

A patient with primary myxedema of the adult type is presented whose admitting complaint of bone pain and x-ray evidence of a lytic lesion in the right femoral head presented a diagnostic problem.

After exclusion of alternate diagnostic possibilities and observation of the effects of thyroid therapy on the lesion, it is felt that the relationship of the bone disorder to myxedema is probably more than coincidental.

The distribution and pathogenesis of bone changes in childhood and adult myxedema and their possible relationship to the case presented were discussed.

Such a lesion in adult myxedema has never been reported in the world literature, and since it could be confused with more serious diseases, it was felt that our case should be reported.

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Gastric Carcinoid Tumor

An Unusual Cause of Hematemesis

RICHARD SCHOENFELD, M.D.; JULES CAHAN, M.D., and ROBERT DYER, M.D., Washington, D. C.

Carcinoid tumor of the stomach is a relatively rare lesion. There have been 42 documented cases reported in the literature, but 16 of these were incidental findings at necropsy examination. There have been no reported cases diagnosed preoperatively. In a recent study, pathological diagnosis of stomach lesions over a 20-year period are reviewed.[1] In this series were 1,235 cases of gastric carcinoma, 38 gastric leiomyomas, and 5 gastric carcinoids.

There is apparently no sex-linked incidence, since 19 of the reported cases occurred in males and 21 in females. (The other was not reported.) The youngest instance occurred in a 15-year-old girl and the eldest in an 89-year-old man. The average age of all of the cases, excluding those found incidentally at necropsy, is 48

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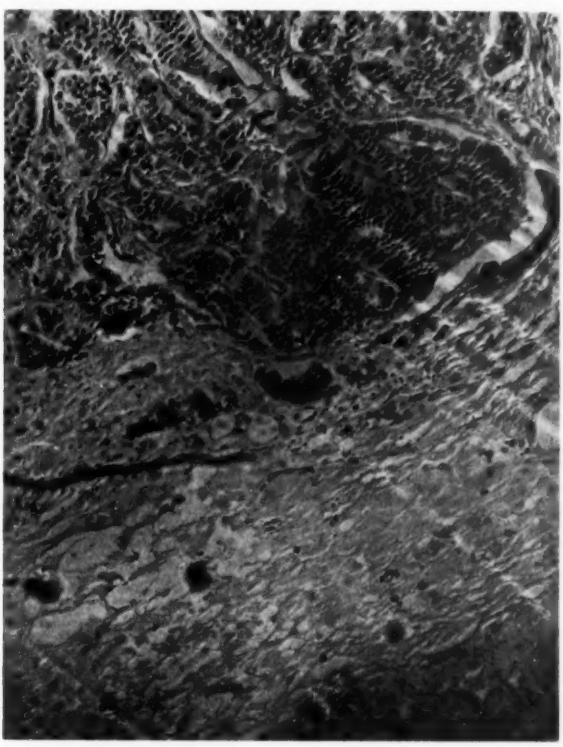
Dr. Jerome Epstein, consultant in gastroenterology, performed the gastroscopies, and Dr. William Newman, clinical pathologist, gave permission for reference to the surgical biopsy.

Intern in Medicine (Dr. Schoenfeld), Assistant in Surgery, Department of Surgery (Dr. Cahan), Assistant in Medicine, Department of Medicine (Dr. Dyer), George Washington University School of Medicine.



Gastric carcinoid tumor. Photomicrograph of the stomach; hematoxylin and eosin stain.

TABLE 1.—*Location and Size of Gastric Carcinoid Tumors*

Site	No.	%
Lesser curvature	8	19
Greater curvature	6	14
Antrum	5	11
Fundus	5	11
Prepyloric	4	10
Pyloric	3	7
Cardia	2	4
Multiple	1	2
Not reported	8	22

TABLE 2.—*Prevalence of Symptoms of Gastric Carcinoid Tumor*[1-5,7-16]

Symptom	No.	%
Pain	14	33
Vomiting	6	14
Weight loss	7	17
Melena	5	12
Hematemesis	5	12
Ulcer symptoms	4	10
Anemia	3	7
Indigestion	1	2
Obstruction	1	2
Anorexia	1	2
Constipation	1	2
Mass in abdomen	1	2
Weakness	2	4
Dysphagia	1	2
X-ray findings only	1	2
None	16	40 *

* The 40% consists of the cases diagnosed incidentally at the time of the necropsy examination

years.[1] In contrast, the average age at the time of diagnosis of appendiceal carcinoids is 29 years and small intestinal carcinoids, 57 years.[1] Gastric carcinoids constitute 8% to 10% of all extra-appendiceal carcinoids.[2]

The size of the reported lesions varied from 3 mm. to 11 cm. in diameter.

Metastasis and Carcinoid Syndrome

The incidence of metastasis to regional lymph nodes and/or distant sites from extra-appendiceal carcinoids is generally reported to be 20%.[10-12] The metastasis rate for appendiceal lesions is 10%.[13] In the 41 cases of gastric carcinoid, metastasis was noted in 11 (27%); no metastasis in 23 (56%), and not noted in 7 (17%).[1] In a recent survey of 79 cases of the carcinoid syndrome, not one primary lesion in the stomach is reported.[13] Many gastrointestinal tract carcinoid tumors metastasize, and some of them produce a symptom-complex referred to as the carcinoid syndrome. This syndrome is due to a disturbed tryptophan metabolism with hyperproduction of 5-hydroxytryptomine. The larger part of circulating 5-hydroxytryptamine is excreted as 5-hydroxyindolacetic acid in the urine, which can be determined quantitatively or qualitatively by physical or chemical methods. In blood, blood fractions, and tissue extracts, only traces of 5-hydroxyindolacetic acid (5 HIAA) have been noted.

Certain biochemically active carcinoid tumors have been investigated.[13] The finding of an abnormally high concentration of 5-hydroxytryptamine or 5-hydroxyindolacetic acid in the tumor tissue, blood, or the urine of a carcinoid patient is usually sufficient to ascertain that the tumor is biochemically active. However, all gastrointestinal carcinoid tumors are not necessarily biochemically active. The presence of unbound 5-hydroxytryptamine in the arterial blood probably causes the flushing, blotchy cyanosis, palpitations, bronchoconstriction, changes of the respiratory rate and depth, hyperperistalsis, intermittent local edema, facial hyperemia, telangiectasia, signs and symptoms of valvular heart disease, joint signs, and symptoms noted in the carcinoid syndrome.[15]

The commonest symptom of gastric carcinoid tumor is pain, which is usually localized in the epigastrium or the right upper quadrant of the abdomen. It often follows the pattern of the pain found in association with benign peptic ulcer. The pain of gastric carcinoid tumor often has a poor response to antacids and antispasmodics. Vomiting and weight loss are the next commonest symptoms, while gastrointestinal bleeding manifested by melena or hematemesis are slightly less frequent. Bleeding is usually not very severe and is readily controlled. Only three patients presented with an anemia.[1,9,14]

Therapy

It is generally agreed that because of the poor results from medical management and

TABLE 3.—*Therapy* [1,2-5]

Therapy	No.	%
None	17	42
Subtotal gastric resection	13	31
Local resection	9	21
Exploratory laparotomy only	2	4
Total gastrectomy	1	2

owing to the rather high malignant potential of these lesions, the primary therapy of gastric carcinoid tumor is surgical. There is still considerable controversy as to which surgical procedures are most justified. Of the 42 reported cases, 17 received no surgical treatment. However, 16 of these were the cases found on necropsy examination. One patient was treated medically and apparently lost from follow-up study. In two patients, an exploratory laparotomy was performed without definitive corrective surgery. One patient had a total gastrectomy; 13 underwent subtotal gastric resection, while 9 underwent local wedge resection. The results with various types of irradiation therapy were generally disappointing.

Prognosis

There are no adequate figures available defining the ultimate prognosis of these cases or evaluating the various surgical procedures.[4] The prevailing opinion is that the lesions are relatively slow growing when they metastasize and that they can exist many years before metastasis does occur. The danger of severe gastrointestinal hemorrhage, perforation, obstruction, or anorexia is generally minimal.[1,14]

Report of Case

A 40-year-old white housewife and waitress was admitted to the George Washington University Hospital on Sept. 17, 1958, with the chief complaint of black, tarry stools of two days' duration. The patient was relatively well until 1953, when she noted the gradual onset of epigastric pain and right upper quadrant abdominal burning before meals and at bedtime, relieved by bland foods and exacerbated by fried and spicy foods. She also complained of increasing flatus, diarrhea, and general malaise. Physical examination, laboratory studies, cholecystography, barium enema, and upper gastrointestinal series were all within normal limits at this time. In 1954, she presented at the psychiatric outpatient clinic with the same symptoms, and the diagnosis of hysteria and anxiety reaction was made. Six months later, she was hospitalized at another hospital for melena and hematemesis. She required multiple blood transfusions, and her condition was diagnosed as duodenal peptic ulcer, although roentgen examinations were again within normal limits.

She presented on several occasions during 1955 and through 1957 in the outpatient clinics with the complaints of epigastric burning, nausea, and flatus. Laboratory studies, stools, and diagnostic roentgenography were repeatedly negative. Attempts at conservative medical management with diet, antispasmodics, antacids, and sedatives were generally unsatisfactory. The patient admitted that she was not following the regimen closely. The past history, review of systems, family history, and social history were essentially noncontributory, except that the patient's husband was an alcoholic and the family had socioeconomic problems in the support of five young children.

On physical examination, the patient appeared neither acutely nor chronically ill. Her blood pressure was 120/80; pulse, 80, and the entire examination was within normal limits.

Admission laboratory studies revealed the hematocrit of 34; hemoglobin 11; white blood cell count and urinalysis within normal limits; sulfobromophthalein retention 0%; blood urea nitrogen 16; sodium 140, potassium 4.2, and chloride 110 mEq. per liter. Gastric analysis revealed strongly positive free and total gastric acid. The fasting gastric sample was guaiac negative. A gallbladder series and barium-enema study were within normal limits.

An upper gastrointestinal series, on the second hospital day, was within normal limits. On Sept. 23, gastroscopy revealed a round ulcer on the lesser curvature of the stomach, 2-3 cm. above the entrance to the pyloric canal. It was approximately 2.5 cm. in diameter; the edges were raised and the base necrotic. The rugal folds did not enter the ulcer. A repeat upper gastrointestinal series the following day was again negative.

The patient was continued on an intensive medical ulcer regimen, and on Oct. 8 a repeat gastroscopy demonstrated the ulcer to be approximately the same size; the edges were higher and the base slightly less necrotic. She was transferred to the surgical service. At the time of exploratory laparotomy, Oct. 15, the examination of the duodenum and pylorus was entirely normal. The stomach was examined, and no lesion could be found by inspection of the serosal surface or by palpation of the organ. Accordingly, a gastrostomy

was performed and a palpable elevated lesion was noted on the lesser curvature of the stomach. Grossly, the mucosa over the lesion was ulcerated, but no active bleeding was noted. A portion of the mass was excised, and frozen section revealed the histologic diagnosis of carcinoid tumor. A subtotal gastric resection was performed with excision of the surrounding lymph nodes. A Billroth I anastomosis was established. Permanent histological sections confirmed the diagnosis and revealed metastasis to one of the four nodes excised from the region of the lesser curvature. The patient's postoperative course was uneventful. Several urinalyses for 5-hydroxyindolacetic acid were negative. She was discharged on Oct. 25 and has subsequently been followed closely in the outpatient clinic, where she has continued to progress satisfactorily on a modified ulcer regimen; she has returned to work.

Conclusion

A case of intermittent hematemesis and melena with peptic ulcer symptoms for at least five years prior to discovery of a gastric lesion on gastroscopy is described and the pertinent literature briefly reviewed. The importance of performing a gastrostomy incision in an attempt to find a bleeding point or lesion is also demonstrated. The lesion at the time of surgery was undetectable by careful examination of the stomach externally, by inspection and palpation. In a recent case report, even though the stomach was opened, carcinoid tumor was undetected.[11] Undoubtedly, our patient's life was prolonged by the gastroscopist's discovery of the lesion, which brought her to surgical exploration.

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Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. Archives of Internal Medicine, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

Hippocrates and the Plane Tree on the Island of Cos

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Beside a fountain's sacred brink we raised
Our verdant altars, and the victims blazed:
'Twas where the plane-tree spread its shades around,
The altars heaved; and from the crumbling ground
A mighty dragon shot, of dire portent;
From Jove himself the dreadful sign was sent.
Straight to the tree his sanguine spires he roll'd
And curled around in many a winding fold. . . .
Iliad ii[1]

The small Greek island of Cos bears some of the most remarkable links between Hippocrates and the modern world. In addition to the ruins of a great temple of Aesculapius, there stands an ancient plane tree under whose shade Hippocrates may have sat and taught his students. Since the basis of this tradition and the relationship of the man to the temple are not well known, it seemed worth while, after a visit to Cos, to review some of the data available on this subject.

It is almost certain that a physician of considerable stature lived during the fifth century B. C., that his name was Hippocrates, and that he was a native of Cos, for both Plato and Aristotle refer to him as their contemporary. The former mentions "Hippocrates of Cos, the Asclepiad" as a teacher of medicine (Protagoras, 311 B)[2] and discusses the philosophy of "Hippocrates the Asclepiad," namely that "the nature . . . of the body can only be understood as a whole" (Phaedrus, 270 C-E).[2] Aristotle suggests his great reputation when he writes ". . . one would pronounce Hippocrates to be greater, not as a human being but as a physician, than someone who surpassed him in bodily size." (Politics VII, iv).[3] However, no biography by a contemporary of Hippocrates exists. Francis Adams and W. H. S. Jones cite only three biographies, all written long after the death of Hippocrates.[4,5] The following sketch of his life, compiled from several translations and interpretations of these biographies[4-12] is probably as much legend as it is fact.

Hippocrates lived during the Golden Age of Greece, and, in addition to Plato and Aristotle, his contemporaries included Pericles; the historians Herodotus and Thucydides; the poet Pindar; the playwrights Aeschylus, Sophocles, Euripides, and Aristophanes, and the sculptors Polycleitus and Pheidias.[13] He was born on Cos, in 460 B. C., just nineteen years after the Persians had been driven from Greece, and in his lifetime he was to see the Peloponnesian Wars and the fall of the great civilization of Athens. His birthday, the 27th of Agriamus in the year of the 80th Olympiad,[6] was celebrated as a festival in his

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honor by the Coans. He studied medicine at Cos, where he lived until the death of his parents. With increasing renown among his contemporaries, he traveled extensively through the cities of ancient Greece. Some say he was able to reduce the mortality during the plague of Athens in 430 B. C., but Thucydides [14] says that all of the physicians of that time were helpless in the face of this pestilence. Hippocrates saved his native island from attack by the Athenians by enlisting the help of Thessaly, a deed for which he was honored by the Coans. He died somewhere between his eighty-fifth and one hundred ninth birthdays, and was buried in Thessaly. Legend has it that a swarm of bees, whose honey was effective in the treatment of children with thrush, settled on his tomb.

Hippocrates was a member of a group of physicians called Asclepiadae and, with them, traced his ancestry to Aesculapius, the son of Apollo; he claimed to be the nineteenth descendant of the god of medicine.[6] (His father was a physician of the same name, indeed Kalopothakes identified twenty-three men named Hippocrates in ancient Greece. Seven of these were physicians of the Asclepiadae of Cos, but only one was the Great Hippocrates.[7] The exact relationship of the Asclepiadae to the temples of Aesculapius is not known. Jones suggests three possibilities which are not mutually exclusive: that the Asclepiadae were the priests of the temples, that they were a clan of hereditary physicians, or that they were a guild of physicians, tracing their origin to Aesculapius and bound by the rules defined in the Hippocratic Oath.[4] Adams describes the medicine practiced at the temples by saying, "Every means that could be thought of was used for working upon the imagination of the sick, such as religious ceremonies of an imposing nature, accompanied by music, and whatever else could arouse their senses, conciliate their confidence, and in certain cases, contribute to their amusement." [5] Edelstein states that although Greek medicine was influenced by religious ideas it rejected magic as useless and wrong.[15] The system of "rational experience and common sense" [5] described in the writings of Hippocrates is free of direct attacks on the temples, and the apparent reverence of the Asclepiadae for the gods of medicine is seen in the Oath, which begins with invocations of Apollo and Aesculapius. Both Strabo (XIV. ii. 19)[16] and Pliny (XXIX. iv)[17] state that Hippocrates obtained some of his medical knowledge from narratives of cures that were inscribed in the temple of Cos. The close

Fig. 1. — Hippocrates' plane tree in the central square of Cos, August, 1958.

link between the practical medicine of the Greeks and their temples is further demonstrated by their physical proximity. The school of Cnidus, as that of Cos, was near a temple, and the ruins of baths were found at the site of the temple of Cos.[12] A hereditary and guild-like structure within the Asclepiadae is suggested by the Oath, which defines the obligation of the physician to "impart precepts, oral instructions and all the other learning to the sons of my teacher, and to the pupils who have signed the indenture and sworn obedience to the physicians' Law, but to none other." [18]

The Hippocratic collection was copied and translated for almost 1,500 years, the oldest existing manuscript being from the tenth century A. D.[4] This does not fully explain the variations among these writings attributed to Hippocrates, and there is no doubt that they represent the work of more than one man.[19] Jones suggests that the Hippocratic collection was the library of the Asclepiadae of Cos.[4] He points out that one of the acts attributed to Hippocrates by his biographers was the burning of a library either at Cos or at Cnidus, the medical school on the mainland just across from Cos. This could represent an attack on ancient superstitions and writings with their replacement by Hippocrates' own observations and ideas. The subsequent growth of such a library with the additions made by his pupils and followers could have contributed to the variations in form and content now found in the works attributed to him.

It was hoped that the excavations at Cos early in this century would reveal evidence of the flourishing cult of Aesculapius at the time of Hippocrates. However, no tablets or inscriptions dating from the time of Hippocrates have been found as yet.[12] The earliest altar to Aesculapius which has been uncovered was erected after 350 B. C., and the great temple was built in the third century B. C.[20] By the second century B. C., coins from Cos bore the portrait of Aesculapius leaning on the serpent staff, and in the early years of the Roman Empire, a Coan coin showed a seated figure and the inscription ΙΠΠΟΚΡΑΤΗΣ.[21]

The plane tree of Cos has become firmly linked with Cos' most illustrious citizen, a natural happening in view of the great antiquity of the tree and the reverence with which the islanders regard Hippocrates. The tree has lent itself to many legends, having been thought to be a tree under which St. Luke and St. Paul rested and even considered to be the oldest living tree.[22] The former is probably incorrect; the latter is certainly false.[23] The exact age of the tree is uncertain but Hermocrates, who visited Cos in the fourth century B. C.,

Fig. 2.—View of the Temple of Aesculapius on Cos taken from the upper of the three terraces. The temple was almost totally destroyed by earthquakes and has been partly restored. The coast of Asia Minor is visible in the distance.

mentions a plane tree under which the inhabitants of Cos had placed a bronze statue of a famous singer.[4] Pausanias, the famous Roman traveler of the second century A. D. describes sixteen celebrated plane-trees[23] and notes the altars of Aesculapius and the olive groves on Cos, but he fails to mention this plane tree.[24] An earthquake in 365 B. C. destroyed the old town of Cos, and the citizens rebuilt the town at a different site.[25] This event, occurring ninety-five years after the birth of Hippocrates, would require the acceptance of the most extreme estimate of his age to permit the physician to have passed beneath the tree that stands in the center of the present city of Cos. There is, however, another possible validation of the local tradition—that the present tree was started by the builders of the new city of Cos from a slip of the tree that stood in the destroyed city. This is not unlikely, since the Aryan peoples of the Eastern Mediterranean revered the plane tree in a manner similar to the worship of the oak in Western Europe (introduction). Menelaus is said to have planted a plane tree as a memorial when he sailed against Troy,[23] and Herodotus (VII. 31)[26] describes an incident during the march of Xerxes through Asia Minor when "he found a plane-tree so beautiful, that he presented it with golden ornaments, and put it under the care of one of his [guard of] immortals." The reverence of the Coans for the tree was noted by de Choiseul Gouffier, who visited Cos in 1776[27] and was struck by "a prodigious plane-tree in the center [of the town that] overspreads the whole [square] with its branches. Bending under their own weight, these might suffer without the attention of the inhabitants who regard the tree with a kind of a religious reverence. . . . The props which support the decrepit limbs of this respected tree are magnificent columns of marble and granite." (The columns were taken from the ruins of the temple of Aesculapias.) In 1841, Ross described it as the "ancient tree under which Hippocrates, according to the tradition of the Coans, often rested."[12] In 1906, a traveler reported that the local sultan had placed the tree under guard day and night with strict orders that no one was to touch the tree.[22] Since World War II, when Cos was returned to Greece, the island has been open to tourists and is now visited by many of the steamship tours of the Greek Islands.

At the present time, the tree is flourishing in the hot Aegean sun; the main trunk is almost ten feet thick, and the twisted limbs are supported by poles and newly built marble pillars. The square in which it stands is resplendent with hibiscus, bougainvillaea, and red and white oleander. Though this may not be the tree under which Hippocrates taught, the tradition is surely worth maintaining, and the tree should remain a living memorial to the greatest of the Greek physicians.

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Contributions of Basic Science to Modern Medicine

Importance of Chemical Transmission in Cardiology and Neuropharmacology

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The evidence for chemical transmission, or for neurohumoral mechanism, as the late Dr. Cannon at Harvard has called it, goes back to Claude Bernard, who observed that fatigue and block produced by curare were localized at the junctions between the nerve fibers and the excitable cell. Very soon after that, in 1877, DuBois-Reymond recognized the possibility of chemical transmission between the nerve cell and the receptor and found that this may be the result of the liberation of a chemical stimulant rather than of an electrical process. After that, it was recognized that some of the actions of the autonomic nervous system could be duplicated by drugs. Probably the first example of this was the finding that muscarine applied to the frog's heart caused a slowing of the rate very similar to that produced by stimulation of the vagus nerve. We all have become familiar with the term "muscarinic action" of acetylcholine, which has originated from this observation. In 1895, Oliver and Schafer first discovered the astonishing activity of the extract from the suprarenal gland and Langley demonstrated the remarkable similarity of the extract to that evoked by stimulation of the sympathetic nervous system. Thus, in addition to muscarine, a second drug had been found which stimulated the action of nervous activity. At that time, the end of the 19th and beginning of the 20th century, work of great importance commenced, which correlated the anatomical pattern of the involuntary or autonomic nervous system to its physiologic effect on smooth muscle and blood vessels. Langley's work led to the recognition and the division between the sympathetic and the parasympathetic system. It was a postgraduate student at Cambridge, T. R. Elliott, who, in 1905, on Langley's suggestion, extended the comparison of the effect of the adrenal extract with those of the sympathetic nerves over a wide range of organs and species; this is a remarkable paper with many a prophetic suggestion. From then on the idea took root that the sympathetic nervous system releases epinephrine or a substance with similar properties. It was also considered likely that the parasympathetic system releases a substance similar to muscarine, but tangible proof was, as yet, lacking. At this time, the stage was not set for recognition of the importance of chemical transmission.

All this changed when Loewi made his experiments. This research brought us experimental facts in place of half-discredited speculation. Loewi's discovery of the possible role of a chemical mediator by the vagus endings in the heart is, of course, familar, but I should like to repeat that although the idea must have occurred to him

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many times, it first took tangible form when he awoke from sleep with the idea of performing an experiment in which two frog hearts could be perfused in series; by stimulating the vagus nerve of the first heart, the release of a chemical substance by the vagal endings could be detected by its action on the second heart. It did not take him long to translate his idea into experimental action and to prove that nervous stimulation resulted in the release of a chemical substance. It was due primarily to the result of the extensive investigation of Sir Henry Dale that acetylcholine was identified as the chemical transmitter substance of the parasympathetic system as well as at the level of the ganglion itself.

It is now well known that there are two main families of chemical agents responsible for the action of the sympathetic and parasympathetic nervous system: (1) norepinephrine (arterenol) and (2) acetylcholine, with its muscarinic and nicotinic action. Dr. Walter Cannon, the late Professor of Physiology at Harvard, believed that there may be an excitatory and inhibitory substance released at the nerve endings. In 1904, a new compound, norepinephrine, was isolated, and its first biological properties were described. In 1946, it was finally shown to be a natural component of the body. It should be mentioned here, however, that even before that date it was considered a tentative candidate for sympathetic nerve transmission. Sir Henry Dale, in 1911, wrote, "In these respects (relation of motor and inhibitory effects and the antagonizing effect of ergotoxin) the action of some of the other bases, particularly of the amino and ethylamino bases of the catechol group corresponds more closely with that of the sympathetic nerves than that of adrenine." Finally, proof that norepinephrine was actually the specific agent of sympathetic nerves was provided by experiments which showed that extracts of such nerves and of organs supplied by them contained appreciable quantities of norepinephrine. In 1947, German workers found that urine contained conjugated norepinephrine and that extracts of mammalian suprarenals seemed to contain the same substance. It was therefore established that norepinephrine is a constituent of the body and that it is, in all likelihood, the chemical transmitter of the sympathetic nervous system.

Before I discuss the other substances which play a role in the chemical transmission, either in the nervous system at the synaptic level or at the myoneural junction, a few words should be said about the formation and destruction of norepinephrine and acetylcholine. Interesting work in this line has been done at the National Institutes of Health. The data were obtained on patients with pheochromocytoma. In those persons, the adrenal glands produce excess quantities of norepinephrine and epinephrine, and because of this, the formation of these compounds can be more readily studied. The steps that occur in the pathways of the formation of tyrosine metabolism and the formation of norepinephrine and epinephrine were first postulated in 1939 by Blaschko, but the advent of radioisotope techniques has made this pathway clear and has placed it on a sound foundation. It has now been demonstrated in animals that C^{14}-labeled phenylalanine gives rise to tyrosine C^{14}, from which 3,4-dihydroxyphenylalanine (dopa) C^{14}, dopamine C^{14}, norepinephrine, and epinephrine are formed. Dopa is decarboxylated by the action of a dopa decarboxylase. Adrenal glands are rich in this enzyme. The formation of these compounds in vitro was also studied on pheochromocytoma tissue obtained from patients with these tumors. Significant radioactivity appeared in norepinephrine isolated from the incubation mixture in all experiments.

With an ingenous technique, these pathways were confirmed in patients with pheochromocytoma. This was accomplished by injecting C^{14}-labeled dopa or dopamine, collecting the urine, and determining the amount of norepinephrine that had been labeled with C^{14}. Within the first hour after the injection of C^{14}-labeled dopa, C^{14}-labeled

norepinephrine appeared in the urine. This suggested very rapid turnover rates. While dopa is rapidly converted into norepinephrine, the injection of C^{14}-labeled norepinephrine does not result in an appreciable appearance of labeled epinephrine, and so the last step of this process is obviously irreversible.

As is to be expected, the adrenal gland is not the only structure in the body to form norepinephrine from its precursors. The sympathetic ganglia and nerve endings possess the same property.

The mechanism of the destruction of norepinephrine and epinephrine in the body is of great physiologic importance. About 20 years ago, Hare found an enzyme in the body which destroyed tyramine. This enzyme converted amines into aldehydes with the formation of ammonia and water. It is an oxidative process. This monoamine oxidase deaminates and destroys epinephrine, tyramine, dopamine, and particularly serotonin, or 5-hydroxytryptamine. The aldehydes which are thus formed are highly unstable. Since the monoamine oxidase possesses a sulfhydryl group, the enzyme is inhibited by organic mercurial compounds. The monoamine oxidase is present in many organs such as the liver, kidney, intestines, brain, blood vessels, placenta, and lungs, but it is absent in erythrocytes, and skeletal muscle contains only very low concentrations. The enzyme appears to be located in the mitochondria.

Amine oxidase is not the only enzyme which destroys norepinephrine. In 1957, Armstrong, McMillan, and Shaw reported the isolation of 3-methoxy-4-hydroxy mandelic acid from human urine and showed that it was a major product of norepinephrine metabolism. Axelrod found that the 3-hydroxy position of norepinephrine can be methylated by animal tissue; an enzyme must therefore be present which accomplishes this. Evidence was presented that O-methylation followed by oxidative deamination is the major pathway of metabolism in certain animal species. The two pathways terminate with the production of 3-methoxy-4-hydroxy mandelic acid. Which of these pathways predominates in man? It would appear that the adrenal gland prefers the mechanism of O-methylation and that the major metabolites in man are normetanephrine and 3-methoxy-4-hydroxy mandelic acid. The presence of these substances in urine may turn out to represent an important diagnostic tool in the recognition of pheochromocytoma. These studies have been amply confirmed by a variety of workers, such as Kirschner and Sjoerdsma, who originally proposed them. Axelrod found normetanephrine in the brain as well as in the adrenal gland. The same author found that adenosyl methionine is necessary as the methyl donor.

The formation of acetylcholine appears less complex. According to Nachmansohn, acetylcholine is formed through the actions of choline acetylase, which acetylates choline. ATP is necessary for this process. Actually, the first step of acetylation in animal cells is the formation of acetyl coenzyme A to acetyl kinase. Choline acetylase transfers the acetyl group from acetyl coenzyme A to choline. Acetylcholine is destroyed by the enzyme cholinesterase. There is really not one cholinesterase but a family of enzymes which differ in different species and tissues. The enzyme which has the highest affinity for acetylcholine is called specific, or true, cholinesterase and should be differentiated from the nonspecific or pseudocholinesterase in blood and tissues. The activity of these enzymes at the site of ganglionic and neuromuscular transmission is sufficiently high to remove, within the limits of the briefest period, the acetylcholine released by nerve impulses.

Acetylcholine, released, combines with the receptor of the nerve endings of the myoneural junction, which is presumably a protein. It is of interest that in the resting condition acetylcholine is present but does not produce excitation; this is probably owing to the fact that it is bound and in an inactive form. Tentatively, it may be called

the "storage form." It is very likely that norepinephrine, as present in the tissues, is bound and in "storage form" without producing a physiologic or pharmacological effect. When the ester is freed, however, it acts upon the receptor, presumably a protein, and this action is responsible for the change in ionic permeability and the generation of bioelectrical phenomena, which will be discussed later.

Until about five years ago, physiologists, pharmacologists, and neurologists were content to deal with three chemical transmitting agents, norepinephrine, epinephrine, and acetylcholine. To the detriment of the psychiatrist and neurologist, however, the list of agents which may be called chemical transmitters has increased. These will now be discussed.

Foremost among them is γ-aminobutyric acid (GABA). Washington University has a special interest in this compound because it was described here by Drs. Roberts and Frankel simultaneously with Awapara and Udenfriend, of the National Institutes of Health. GABA is formed from the decarboxylation of glutamic acid by the pyridoxine (vitamin B_6)-dependent enzyme L-glutamic acid decarboxylase. Glutamic acid itself is formed by deamination of α-ketoglutaric acid. The formation of GABA represents an accessory cycle to the Krebs tricarboxylic acid cycle, with α-ketoglutaric acid aminated to form glutamic acid and glutamic acid decarboxylated to form GABA; GABA is then transaminated with more α-ketoglutaric acid and hydrated to form succinate. Glutamine, which is formed from glutamic acid, is the only substance that crosses the blood-brain barrier; it thus represents the mechanism for replenishment of substrates for the tricarboxylic acid cycle from circulating substances in the brain. It should be mentioned at this point that the convulsions produced in animals by the injection of large doses of isoniazid (INH) result in reduced levels of GABA in the brain. Apparently, INH lowers the levels of GABA by inhibiting L-glutamic acid decarboxylase; this enzymatic inhibition can be reversed by the administration of pyridoxin. A recent report seems to indicate that GABA increases oxygen uptake of slices of cat cerebral cortex, suggesting that it serves as a substrate for oxidative metabolism of the cerebral cortex.

Two more compounds remain on our list as possible chemical transmitter agents. They are serotonin and lysergic acid diethylamide. The discovery of serotonin, or 5-hydroxytryptamine (5HT), has been the result of a long history of hide and seek. It has been observed by a great many workers, including ourselves, that blood, particularly shed blood, has marked vasoconstrictor properties. The kidney is most vulnerable to the vasoconstrictor activity of shed blood. These substances which were thought to be responsible for this property were named "vasotonins." It was thought at that time that vasotonins originated from blood platelets. Our investigation, which dated back to 1938, showed the vasoconstrictor effects of shed blood and demonstrated, confirming the work of others, that the lung inactivates these constrictor substances. The discovery of serotonin and its identification was finally accomplished in 1947, by Rapport et al.

Hydroxytryptamine (5HT) originates by hydroxylation and decarboxylation of the amino acid tryptophan and is destroyed by amine oxidase and dehydrogenase. It is known that only 1% of the total pool of tryptophan is converted into serotonin. In the presence of carcinoid, much larger amounts of tryptophan are used for the formation of serotonin (about 60%). The formation of 5-hydroxytryptamine, or serotonin, is particularly abundant in the gastrointestinal tract and in the central nervous system. The 5HTP content of blood platelets is high because these elements act as carriers. Monoamine oxidase, which destroys serotonin, is present in large concentrations in the central nervous system. The affinity of monoamine oxidase for serotonin is greater than that for other catecholamines.

The substance originating from deamination of 5HT is 5-hydroxyindolacetic acid, which is known to be excreted in the urine in large amounts in patients with the carcinoid syndrome. Therefore, the excretion of this acid is a good indicator for the activity of monoamine oxidase and has been widely used in the investigation of the activity of this enzyme. Interestingly, the portions of the brain which contain an increased amount of serotonin are also particularly abundant in norepinephrine.

Lysergic acid diethylamide (LSD) belongs to a large group of substances which now have been termed psychotomimetic or psychotogenic. These terms indicate the production of schizophrenic, psychotic-like stages. We are but the latest of generations of experimentalists who, from before the dawn of history and in every part of the world, have tried to alter, explore, and control the working of the mind. The history of 5,000 years of futile searching of the Indians, Siberians, Africans, etc. has shown a multitude of substances which produce hallucinations. To mention a few, there are soma, hashish, cohoba, caapi vine, and the fungus teononacatl. LSD was discovered by chance in the research laboratory of the Sandoz Company in Basel, Switzerland, on April 16, 1943. The circumstances surrounding this discovery were fascinating and represent a fine example of serendipity. One afternoon, A. Hofmann noticed a peculiar sensation of vertigo and restlessness while working in the laboratory. In a dream-like state he left for home. There was a peculiar state of drunkenness characterized by exaggerated imagination. "With my eyes closed, fantastic pictures of extraordinary plasticity and intensive color seemed to surge towards me." After about two hours, this effect passed off and he felt normal. He had been working with *d*-lysergic acid diethilamide, a substance synthesized in 1958 by him and Stoll. He had unintentionally inhaled a minute amount of it. Investigators in this field are entirely familiar with the rest of this story, but it is interesting that Hoffmann, in order to convince himself, took a greater amount of it the next day, only to be subjected to more vivid and prolonged hallucinations. Hofmann and Stoll studied the compound thoroughly. The symptoms appeared in about one and one-half hours, reached peak intensity at two hours, and then declined noticeably; they disappeared completely in eight hours. The hallucinations appeared to occur in waves. LSD is an indole compound with tryptamine as central core; this is important, because the structure may be related to the antagonistic character of LSD to serotonin. This led to the belief that the effect of LSD was due to an inhibition of serotonin, but this question will be examined further in this article. LSD belongs to the group of ergot preparations which are all derivatives of lysergic acid. There is close relationship between ergonovine and lysergic acid. LSD has central actions (psychic, somatomotor, and automatic nervous functions). The autonomic effects are mainly sympathomimetic. The motor effects are pyramidal and extrapyramidal, leading to ataxia. The psychic effects are well known and have already been described. The direct peripheral effects are weakly adrenolytic, affecting the uterus, blood vessels, and muscles. Its most important pharmacological action is its pronounced antagonism toward 5-hydroxytryptamine (serotonin).

Another well-known psychotogen is mescaline, or peyote; its structure is not too different from the sympathomimetic amines. It is obtained from a cactus plant containing the pharmacological substance. It grows in the United States, particularly in the Rio Grande Valley. It has been used by various American Indian tribes for religious purposes. Peyotism, as this religion is called, believes that God put some of his Holy Spirit into the peyote; the Indian eats the sacramental bread, and wine is often used. It is also considered as a cure-all and is eaten during a ritual ceremony of hymns, dances, and prayers. It does not cause

addiction, and there is no valid evidence that abstinent symptoms occur when the drug is not available. Mescaline is related to epinephrine, norepinephrine, and adrenochrome, as well as to LSD and to tryptamine. The indole ring is present in all of these compounds, although in various combinations. Mescaline is of historical importance, since it was the first drug known to produce hallucinations which appeared to possess definite biochemical activities. According to Quastel, it inhibits glucose, lactate, and pyruvate oxidation by brain. The structural similarity of these psychotogens, such as mescaline and epinephrine, suggested that a disturbance in epinephrine metabolism might produce a toxic catecholamine capable of causing psychoses. Even adrenochrome or norepinephrine in large doses are psychotogens; there is too much smoke not to suspect a fire.

The importance of some of the sympathomimetic amines in cardiovascular diseases arises only in part from their well-known vasoconstrictor properties. Our interest in the connection between norepinephrine and heart muscle arose from studies undertaken in connection with our work on heart failure. The fact that the isolated heart fails within hours has been observed for the first time since Starling and his group found that the efficiency of the isolated heart was considerably diminished as compared to that of the heart in vivo. Many ideas have been proposed to explain this "specific failure of the isolated heart," but there have been no definite conclusions. Heart failure, which one sees in the isolated heart, has some mechanical features in common with chronic heart failure as it occurs in patients with congestive heart failure. In both instances there is an increase in the end-diastolic pressure, dilatation of the heart, and diminution of the stroke volume. However, there are notable differences. In the first place, the element of hypertrophy is missing. Secondly, the oxygen consumption of the isolated heart is diminished, while that of the heart in situ remains at its nonfailing level. It has been shown repeatedly that the oxygen consumption of the heart in congestive failure remains normal. The main difference between the acutely failing heart in vitro and the heart in patients with congestive heart failure lies in the fact that in the former, both cardiac work and oxygen consumption are diminished, while in the latter, the myocardial oxygen consumption remains normal.

What is the cause for the spontaneous heart failure occurring in the heart-lung preparation? Several possibilities exist. The first is that it is the result of alterations of the contractile proteins of the heart. Such studies have been performed on the heart muscle of persons who succumbed to congestive heart failure and on isolated hearts with spontaneous failure. There is a diminution in the contractility of actomyosin obtained from failing human hearts; however, the contractility of actomyosin prepared from hearts failing in the heart-lung preparation remained unimpaired.

Therefore, it is likely that the mechanism of spontaneous failure cannot lie in organs of energy utilization but must be sought in mechanisms connected with energy production. Since the utilization of substrates by the isolated failing heart remains normal, one must look for disturbances not connected with the extraction of substrates or the utilization of metabolites. A clue to the possible mechanism of spontaneous failure may lie in the work of Rein, who showed that the inclusion of liver and spleen in the perfusion circuit of a heart-lung preparation increased myocardial efficiency. It is not clear from these studies whether the spleen actually releases a substance which is transformed by the liver into the active principle. It could be established here, in confirmation of the work of others, that the inclusion of both liver or spleen does increase the myocardial efficiency slightly, primarily by a diminution in the oxygen consumption of the heart. Cardiac work is not altered.

The question arose as to the nature of the active principle or principles in these

organs. Spontaneous myocardial failure in the heart-lung preparation might result from lack of a catecholamine in either heart muscle or the perfusion fluid; the rise in myocardial efficiency resulting from the inclusion of liver and spleen in the perfusion circuit might be the consequence of partial restoration of the depleted supply of these substances by these organs. In dealing with this problem, the question arises, first, which of the catecholamines is the most likely to exert these actions? The answer lies in the relative distribution of the three likely catecholamines; dopamine, norepinephrine, and epinephrine. The content of norepinephrine in most organs far exceeds that of either dopamine or epinephrine. It is known that the spleen contains large amounts of norepinephrine because of its large supply of sympathetic nerve endings. There has never been any evidence for the assumption that norepinephrine is located outside the nervous tissue itself; nor is it likely that the norepinephrine present in the nerve trunk is released under physiologic conditions. However, norepinephrine at the nerve endings has a physiologic function which appears during a nerve impulse. There are considerable amounts of norepinephrine present in spleen, heart, ciliary bodies, and liver. The norepinephrine concentration in the lung is relatively low. The concentration of norepinephrine in these organs appears to be related to their adrenergic nerve supply. Direct determinations have shown that arteries and veins contain large quantities of norepinephrine. Moreover, the amounts found in various layers of the vascular wall bear a clear relationship to the vasomotor supply. Veins also contain considerable amounts of norepinephrine, illustrating the importance of venomotor nerves. The coronary vessels are particularly rich in norepinephrine.

In order to prove that lack of norepinephrine is responsible for the spontaneous failure of the isolated heart and that addition of this catecholamine by the spleen and/or the liver partially counteracts this condition, it is necessary to answer three questions: 1. Does norepinephrine reproduce the effects of liver and spleen on the isolated heart? Does it raise cardiac efficiency by lowering myocardial oxygen consumption without raising cardiac work? 2. Are the catecholamines of the spontaneously failing heart or the perfusion fluid of these hearts depleted? 3. Does the addition of liver and spleen restore the concentration of norepinephrine in the heart or the perfusion fluid? It is known that the infusion of relatively large amounts of catecholamines diminishes the efficiency of the isolated heart; when catecholamines are infused at any fixed cardiac output, cardiac oxygen consumption rises in association with increases in blood pressure and heart rate, while the external mechanical efficiency of the heart declines. The fall in the percentage of oxygen extracted by the heart, the ratio of cardiac oxygen consumption to oxygen availability, and the rise in coronary venous oxygen are all attributable to the direct action of the catecholamines on the coronary vessels.

However, the situation is different when very small amounts of norepinephrine or dopamine are used in these preparations. This results in an increase in the myocardial efficiency, because the oxygen consumption of the heart diminishes while cardiac work is not altered. This confirms previous studies of Krayer.

Is the heart muscle or the perfusion fluid in the heart-lung preparation depleted of norepinephrine? It has been previously mentioned that the heart contains appreciable quantities of norepinephrine. Experiments were performed in which the norepinephrine content of hearts rapidly removed from the animal was compared to that of the heart maintained in the heart-lung preparation for at least one hour. There is no appreciable difference between the two preparations. This finding illustrates that the presence of norepinephrine in the isolated heart does not prevent the development of spontaneous failure. This becomes particularly clear when the concentration of

norepinephrine in heart muscle is increased by the addition of dopa to the perfusion fluid. Already, von Euler has shown that infusion of dopa into animals leads to considerable increase in the concentration of norepinephrine of the heart as well as of other organs. Even after the positive inotropic effect of the conversion products of dopa (dopamine, norepinephrine, and epinephrine) has disappeared and the performance curve of the heart again shows the presence of failure, the concentration of norepinephrine in heart muscle remains elevated. Apparently "stored noradrenalin" does not affect myocardial contractility; similar to acetylcholine, it may be inactivated by special binding to proteins, and only the nerve impulse can establish the link between the amine and the effector organ. Recent information indicates that the catecholamine content in the perfusion fluid of a heart-lung preparation is diminished. One may therefore conclude that the spontaneous failure of the isolated heart results from deficiencies of catecholamines in the perfusion fluid and that the amine content of the denervated heart is ineffective in preventing the development of failure.

One of the striking features of the mechanism of these transmitter substances is their balance and counterbalance. For example, lysergic acid as an essential part of the ergot counteracts the action of the amine, serotonin. Furthermore, an amine oxidase inhibitor blocks the action of this enzyme, resulting in increased concentration of catecholamines and serotonin. In this connection, the action of reserpine deserves special mentioning. When reserpine is given, the final breakdown product of serotonin, 5-hydroxyindolacetic acid, appears in increased concentration in the urine. This suggests that bound serotonin in the body has been released and is now being metabolized. When animals receive a further injection of reserpine, urinary excretion of hydroxyindolacetic remains normal. It has been proposed that the central actions of reserpine are actually mediated through serotonin "antagonism." After intravenous administration of reserpine to rabbits, the drug rapidly enters the brain, achieving its maximal concentration in about 10 minutes. The brain levels then decline rapidly; in about two to four hours reserpine cannot be detected. While the brain levels of reserpine are declining, the pharmacological effect progressively increases, becoming maximal in two to four hours. This occurs at a time when serotonin levels are particularly low. The effect persists for two days; then the level of serotonin increases and pharmacological effects diminish. Thus, certain central actions of reserpine are related in time to the change in concentration of brain serotonin and not to that of reserpine. Shore has therefore proposed that reserpine acts as follows: It rapidly enters the tissues, irreversibly affects the serotonin-binding sites, and then disappears. As a result, serotonin is released and the unstable free form is metabolized by the action of monoamine oxidase. Serotonin continues to be synthesized in the body, and the low serotonin level that persists presumably represents a balance between its rate of synthesis and its rate of metabolic transformation. The effect of reserpine persists until the binding sites regain their binding capacity or until new sites are formed.

The possibility must be considered that, in addition to serotonin, reserpine depletes the tissues of catecholamines such as norepinephrine and epinephrine. This is probably responsible for the action of reserpine on the heart. It has been shown by Krayer that the drug when given in single doses to the heart-lung preparation causes a definite increase in the heart rate of the isolated organ. The effect has the appearance of a continuous infusion of epinephrine or norepinephrine. It is Krayer's opinion that a long-lasting release of epinephrine and/or norepinephrine best explains the phenomenon. In principle, therefore, the effect of reserpine on the catecholamine content of the heart is very similar to its action on the serotonin content of the brain. In both in-

stances, the action of the amine outlasts the detectable presence of reserpine; the pharmacologic action of reserpine is due to the release of the amine. This finding should be considered in the light of the previous discussion that the heart muscle contains catecholamines in "stored" or "inactive" form. Activation of these stores is accomplished not only by sympathetic discharge but also by reserpine. Under these circumstances, the catecholamines are transformed from the stored or inactive into an active form which, released from its bondage, enters the interstitial fluid or the intravascular compartment. The clinical experience of anesthesiologists that patients on reserpine treatment are less able to withstand the effects of anesthesia may be the result of a depletion of these catecholamine stores in heart muscle and peripheral blood vessels. In the heart-lung preparation, release of catecholamines by reserpine has a positive inotropic effect. Krayer showed that the addition of reserpine led to depletion of the heart muscle of norepinephrine and epinephrine.

What is the importance of chemical mediators in peripheral nerves and in the central nervous system? Discussion will be restricted to the following aspects: the localization of the chemical transmitters and the possible relation between chemical transmission and neuron activity.

It has already been mentioned that the sympathetic nerves, the axon as well as the nerve endings, contain considerable amounts of norepinephrine and dopamine. The location of these catecholamines was investigated by Schumann. In this study, homogenates of splenic nerves were divided into three fractions by differential centrifugation. The first fraction containing the large size sediment was discarded. The supernatant fluid then was centrifuged at 12,000 g. The sediment (Fraction 2) contained the cell granules, such as the mitochondria; the supernatant (Fraction 3) contained the cytoplasma with the microsomes. It was found from previous observations that the splenic nerves contain norepinephrine, dopamine, and dopa decarboxylase (von Euler). In the investigation by Schumann, dopamine and dopa decarboxylase were found in the microsomes and cytoplasma. Norepinephrine however, was detected in the cell granules of Fraction 2. Schumann concludes that decarboxylation of dopa to dopamine occurs in the cytoplasma of the nerves. Once dopamine is formed, it penetrates into the cell granules, where it is oxidized to norepinephrine. Epinephrine was not present in any of these fractions. In contrast, granules obtained from the adrenal gland methylated norepinephrine to epinephrine.

These findings confirm that norepinephrine is the only transmitter substance of the sympathetic nerve endings and that there is no conclusive evidence for the role of epinephrine in sympathetic nerve transmission. One should therefore only talk of noradrenergic, not of adrenergic, nerves.

What is the distribution of norepinephrine in the central nervous system? The presence of norepinephrine and epinephrine in the brain has been demonstrated by Raab, von Euler, and others. Vogt, at the University of Edinburgh, studied in detail the individual distribution of catecholamines in the central nervous system. Accordingly, in the diencephalon, the hypothalamus contains very large amounts of norepinephrine. In the medulla, the area postrema has a high concentration. Attempts were made to localize more precisely the site of norepinephrine in the hypothalamus. A definite concentration gradient was found when the hypothalamus was divided into dorsal and ventral parts, the latter containing more norepinephrine than the former. Norepinephrine was not found in either lobes of the pituitary. The cortical areas contained very little norepinephrine, the thalamus itself contained some. As already mentioned, the area postrema in the bulb of the medulla, a tissue devoid of ganglion cells and therefore not part of the brain proper, contains very large amounts. Insulin caused a depression of the norepinephrine content of the hypo-

thalamus, and ether anesthesia reduced that of the area postrema. It appeared that substances which cause a secretion of catecholamines by the adrenal medulla are particularly active in depleting the brain of norepinephrine.

The significance of these findings may be that norepinephrine is concentrated in those portions of the brain which, when stimulated, produce a pressor response. In addition to a pressor effect, it is possible to elicit from the hypothalamus practically all responses mediated by the peripheral sympathetic nerves.

The high concentration of serotonin in the central nervous system has already been discussed. Serotonin (5HT) is present particularly in the diencephalon. These regions are of great importance in the automaticity of regulating vegetative processes. There appears to be a parallelism between the concentration of norepinephrine and those of serotonin. This finding has been thought to point to a correlation between the two amines. Mention has already been made of the close relationship between reserpine and serotonin. Reserpine leads to liberation of 5HT. The liberated serotonin undergoes rapid deamination by amine oxidase. It was stated that the pharmacologic effect of reserpine may very well be due to the disappearance of serotonin. The possible relationship between serotonin and lysergic acid diethylamine has also been mentioned. LSD, an ergot preparation, antagonizes the action of the amines.

Finally, serotonin concentrations in the brain appear to be influenced to a large extent by an amine oxidase inhibitor, iproniazid. Since iproniazid inhibits amine oxidase, it results in an increase in serotonin concentration in the central nervous system. Thus, reserpine leads to a diminution of serotonin while iproniazid leads to an increase. One should keep in mind that inhibition of amine oxidase does not only affect the concentrations of serotonin but also those of catecholamines.

What are the neurophysiologic effects of sympathomimetic amines and other psychotomimetic substances? Several approaches to this problem have been attempted; a study of the effect of synaptic transmission has been particular fruitful. For example, Marrazzi and co-workers found, in their survey of a variety of sites in the nervous system, that a consistent reciprocal relationship existed between excitation or enhancement by acetylcholine and acetylcholine-like substances on synaptic transmission phenomena and inhibition by epinephrine, norepinephrine, and other sympathomimetic amines.

Marrazzi used a simple system of investigating the effect of various drugs on the cerebral synapses. Because the brain is a communication system, it seemed most appropriate to measure function by recording the handling of a test message. This is supplied in the form of a submaximal electrical stimulus applied to one optic cortex in a cat who has received a large dose of pentobarbital sodium. This stimulus initiates a conducted response in the association or transcallosal tract that connects the stimulated point to a symmetrical point in the contralateral cortex, where, after synaptic transmission, the stimulation evokes a cortical potential. This cortical potential in the contralateral cortex can then be recorded and represents the result of synaptic transmission.

Epinephrine results in cerebral synaptic inhibition as indicated by the reduction in the surface negative wave correspondent to outflow, while the inflow is essentially unaltered. The same sort of synaptic inhibition is shown following norepinephrine. It appears that these drugs, together with amphetamine and mescaline, are closely related structurally. Furthermore, they can produce "model psychoses." Epinephrine, with its first oxidation product, adrenochrome, an indole, and lysergic acid diethylamide (LSD 25) can be considered to be built on an indole nucleus; serotonin has a similar structure. Consequently, the epinephrine-like psychotogens are chemically related to the indole-like compounds.

Is there any functional parallelism or neurophysiological correlation with this chemical relationship? Marrazzi and his group, with the use of the synaptic transcallosal transmission from one optic cortex to the other, found that all these structures produce synaptic inhibition identical to that produced by norepinephrine; the degree of inhibition varies so that it required milligrams of mescaline to produce the effects which can be evoked with 1μg. of LSD 25. Serotonin turned out to be the most effective cerebral synaptic inhibitor, being effective in as little as 1μ. doses. Accordingly, Marrazzi believes this indole may represent the type of endogenous substance that is instrumental in bringing about some forms of spontaneously occurring mental disturbances.

Iproniazid, which inhibits monamine oxidase activity, leads to an increase in serotonin concentration in the brain. Serotonin is an inhibitor. Consequently, iproniazid should produce marked inhibition by virtue of its effect on serotonin. Indeed, there is considerable inhibition following iproniazid, as a result of the accumulation of serotonin at the synapses.

This technique of the study of synaptic transmission is useful in an investigation of drugs used as tranquilizing agents. The inhibition produced by mescaline is markedly reduced by the administration of chlorpromazine. This type of tranquilizer appears to act by inhibiting the inhibition of mescaline. Chlorpromazine (Thorazine) alone has no effect on synaptic transmission.

Marrazzi believes, on the basis of these experiments, that there exists an equilibrium of neurohumoral control of transmission in cerebral synapses and throughout the central nervous system; this is susceptible to distortion and imbalance by disturbance in the amount of chemical regulator or the susceptibility of neurons. The psychotogens or psychotomimetic substances which produce model schizophrenia show some resemblance to the well-established inhibitory synaptic neurohumors, such as norepinephrine and serotonin.

The work of Marrazzi has been critically reviewed, and much additional information has been furnished by Rothballer. He mentions the fact that the transcallosal response employed so extensively in the above experiments of Marrazzi was originally thought to represent a simple two-neuron arc, with a surface-positive wave representing the presynaptic impulse entering the cortex from the opposite side (input) and the succeeding surface-negative wave an indication of the postsynaptic impulse presumably leaving (output). According to Rothballer, the interpretation given by Marrazzi is no longer certain, although not necessarily incorrect. The difficulties in interpreting the data are probably due to the "present chaotic state of cortical electrophysiology." Thus, the problem of inhibition produced by epinephrine and norepinephrine remains uncertain. It has, however, been established (Rothballer) that epinephrine in man produces a variety of subjective complaints like restlessness and anxiety, whereas norepinephrine apparently does not. Larger doses of epinephrine or norepinephrine produce a characteristic syndrome of stupor, coming on gradually with long latency and lasting many minutes or hours. This is generally preceded by vomiting, retching, and respiratory stimulation and, depending upon the species, varies in degrees of excitement.

Much has been said in the previous paragraphs about inhibitory and excitatory action of drugs on the central nervous system. The physiological basis for inhibition and excitation of neurons is of great importance in the understanding of the action of these drugs.

Inhibition in the central nervous system, particularly in the spinal cord, is a well-known phenomenon which was extensively studied by Sherrington. One of the most dramatic experiments in physiology described by Sherrington is the inhibition of the crossed-extensor reflex. When a full isolated quadriceps muscle of a decerebrated cat is attached to a myograph, stimulation of the opposite femoral nerve gives rise to

the familiar crossed extensor reflex. When the contralateral femoral nerve is stimulated, the other leg is stretched as if trying to get away from the nociceptive stimulus. If, during the height of the extension of the quadriceps muscle the sciatic or some smaller nerve on the same side is stimulated, the myograph lever drops dead beat to the original resting tension exactly as if the motor nerve had been instantaneously severed. The latency of the inhibition is little more than the duration of twitch contraction of the muscle itself. The knee jerk itself has served as a convenient index of the central inhibitory state. For instance, when knee jerks are evoked at approximately three per second, the inhibitory brake-shock stimulus can be applied at random intervals before and after the tendon tap.

Until recently, the nature of inhibition remained mysterious. As Gasser, in 1937, remarked, "the large number and diversity of the theories about the nature of inhibition and the nervous system may be taken as a measure of the obscurity which has surrounded the subject." Eccles has accomplished a great deal in elucidating central inhibition by the technically extremely difficult task of microelectrode impalement of motor neurons of the spinal cord of the cat. He was able to record the resting and action potential of the membrane of single cells and to determine the effects of excitatory and inhibitory impulses on the synaptic and spike potentials of the neuron. Eccles discriminates between the excitatory postsynaptic potential (EPSP) and the inhibitory postsynaptic potential (IPSP). A single volley in quadriceps afferent fibers evokes a hyperpolarizing response to the inhibitory postsynaptic potential in a motor neuron of the antagonistic muscle (the biceps-semitendinosus). The membrane potential of 66 mv. increases to over 68 mv. The finding that inhibitory impulses produce hyperpolarization of the surface membrane was new and unexpected. De- and repolarization of a nerve or muscle are, according to Hodgkins and Huxley, the result of movements of sodium into and out of the cell; obviously, the inhibitory postsynaptic potential cannot be due to the same ionic changes, because during inhibition the potential becomes more negative. Consequently, one must assume either movements of positive ions out of the cell or of negative ions into the cell. This could be due to the outward movement of a cation, such as potassium; to the inward movement of an anion, such as chloride, or to the combined movements of both cations and anions in these respective directions. All these ionic changes increase the small internal excess of anions, thus giving rise to hyperpolarization. Eccles considered as necessary to postulate that a specific transmitter substance causes the inhibitory synaptic response of the motor neuron by changing the ionic permeability of the subsynaptic membrane. He could show that the membrane becomes highly permeable to Cl^- and K^+ while retaining a high degree of impermeability to sodium ions. Eccles also demonstrated that there is an interplay between excitatory and inhibitory effects. Accordingly, an impulse reaching an excitatory synapse operates by liberating a transmitter substance which causes a brief ionic current of flow inward across the subsynaptic membrane. Correspondingly, the inhibitory impulse liberates a transmitter which causes the subsynaptic membrane to generate a current that tends to hypopolarize the whole postsynaptic membrane.

What is this inhibitory substance? Epinephrine, norepinephrine, mescaline, and even LSD have already been mentioned as inhibitory. According to Kuffler, γ-aminobutyric acid (GABA) may activate the inhibitory mechanism directly. The main point of interest is the specific action of GABA in stopping discharges of the sensory cell by a mechanism, which, in many essential aspects, resembles neural inhibition. Rather than inhibiting by depolarizing, it can also hyperpolarize and move the depolarized membrane toward its resting state. In concentrations used as present, its

effect is largely, but not exclusively, confined to the dentrites, where the inhibitory synapses are located and where stretch deformation acts. However, at present there is no final evidence which establishes GABA as the physiologically occurring transmitter substance.

At the end of this review one may ask why a physician with his primary interest in problems of circulation should spend so much time discussing problems of the physiology of the central nervous system. It must be evident at this point that chemical transmitters such as acetylcholine and norepinephrine are of equal importance in circulatory and neurophysiological events. The common denominator is the innervation of the heart and peripheral vessels by the autonomic nervous system. Any investigator, regardless of his field of primary interest, cannot fail but to recognize the unique interest of excitation and inhibition. Most of the inhibitory substances are chemically related and are mutually antagonistic or synergistic, but the most attractive aspect of this problem is its mystery. For example, little is known of the relationship of norepinephrine to heart failure and to the intrinsic regulation of the coronary circulation. In neuropharmacology it has yet to be established that "model psychoses" produced by some of these substances have more than a casual relationship to some of the clinically encountered mental illnesses. Unfortunately, one of the difficulties is that the tools at our disposal in the investigation of these relationships are still too crude; it may even be that, as Sherrington has expressed it: "Our mental experience is not open to observation to any sense organ. . . . [It] has no such channel of entrance to the mind. . . . The mental act of "knowing" . . . is experienced not observed."

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

The Case for Modern Man. By Charles Frankel. Price, $3.50. Pp. 240, with no illustrations. Harper & Brothers, 49 E. 33d St., New York 16, 1956.

Obsession with the shadow of atomic doom too readily narcotizes us. Despair focuses on oblivion, and a whole people retreats into a conservative posture, searching for security. We are afraid. In such a fetid climate of clammy fear it is like a breath of fresh air, dry and clarifying, to read and study a wise book in defence of the liberal position. Such is Charles Frankel's "The Case for Modern Man." In a society whose weather vanes are blown by such prophets of doom as Jacques Maritain, Arnold Toynbee, Reinhold Niebuhr, and Karl Mannheim, it is a rare pleasure to see the scowling climate of opinion, the foreboding cold front of these critics of the liberal view, called in question in a brilliant and scholarly study. The managerial revolution, the increasing power of federal governments, the strife in America, Europe, Africa, and Asia beset us on all sides. Many men have wondered if the hope for a liberal era was not coming to an end, if not already ended. Toynbee has attacked the secular modern age because of its attempt to construct its own society on humanistic grounds. This, he thinks, demonstrates severe guilt caused by inner pride, for he believes that we are breaking fundamental laws of history. Neibuhr, believing in the all-pervasiveness of original sin, a kind of genetically determined inborn state which is built into the germ plasm of sinful man, rejects the liberal state and with it any possibility that man may be improved or perfected. The evil locked in DNA and RNA is the neocalvinistic equivalent of original sin. Mannheim is opposed to the liberal view because he does not believe in the objectivity of human reason. Maritain, believing in absolutes, objects to the liberal view. He denies the possibility of an experimental attitude in morals.

Against this brooding despair, four black birds on a barren wintry wall, this book brings hope if not cheer. It is encouraging, for it holds that human capacity can mold if not entirely control human destiny. Man's skill, potentially, may thwart his own trickery. Thus Frankel recognizes that for the first time man is in a position to bend the future toward his conception of a better world, though the possibilities of failure loom large before us. This unforced enthusiasm is a healthy sign in a society where pessimism is taken for granted, for here we have a positive statement, one brilliantly set forth by a man who shares with some scientists and physicians a belief that human intellect, properly used, may indeed fashion a better world. Frankel discusses at length doctrinal orthodoxies, such as those of Marx and Freud, comparing them with the beliefs of the founding fathers of the liberal tradition. He goes a long way toward establishing his thesis that our liberal tradition now has greater possible use than ever before.

The essence of the book can be summed up by one of its paragraphs. "There have been modern men in most eras, and there have been other modern eras. At least once before, during the Greek Enlightenment, the Western mind envisaged a world in which the critical spirit would be preferred over the pious spirit, and in which doubt, not dogma, would be regarded as the leaven of a high civilization. Such modernity has been only one strain in the present era, and not always a dominant one. But it has lasted longer, gone deeper, and spread farther than has the modern spirit in any other time. No other age has gone so far in the belief that the spirit of modernity might be widely shared, and that all men might participate in the goods and responsibilities of a modern civilization. The modern spirit in Athens was a brief and glimmering thing, arising in a society based on slavery. The modern spirit in fifteenth-century Italy was an aristocratic phenomenon, limited to an elite. But our own revolution of modernity has led to the unprecedented vision of a society in which the opportunity for personal achievement and social power would be generally diffused among men, and not limited to a selected group."

This is but an example of the challenge to the pessimists which Charles Frankel is able to muster. We are exhorted to believe in man's capacity to improve his lot. We are warned

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that the hard sell of the apostles of doom is echoed by the corruption of psychology and social science in the hucksters of the shabby luxuries we need not, neither do we want. But despite setbacks, the human spirit cannot continue to function in a climate of despair. Existentialism with its callous cynicism or surrender must be attacked by renewed hope, for the quest of the perplexing meanings in life ebbs away when bleak despair overwhelms hope, no matter how small and forlorn hope may be. Today, optimism, rather than pessimism, is the badge of courage, and Frankel shows how man may wear it with dignity in the face of towering impediments, not the least of which is the eternal need for hard work.

WILLIAM B. BEAN, M.D.

Men and Books: Sir William Osler. Earl F. Nation, M.D. Price, not given. Pp. 67, with no illustrations. Privately printed at the Castle Press, Pasadena, Calif., 1959.

While Osler was Regius Professor of Medicine at Oxford, in 1912, he was prevailed upon by his friend, Dr. Andres McPhail, the recently appointed editor of the *Canadian Medical Association Journal* for some "thunder." At fairly regular intervals for three years, until World War I began, the "books and men snippets," as Osler called his thunder, illuminated the pages of the journal. Osler's wide-ranging fancy included such diverse essays as "The Funeral of Lord Lister," "Two Frenchmen on Laughter," "Dr. Slop," and "John Shaw Billings." In each essay, there is some characteristic turn which adds to the charm. Some years ago, I obtained back copies of the *Journal* and had these biographical essays bound for my personal use. Now the entire group has been collected in a single volume, which all Osler devotees should get hold of if they can. The volume, edited by Dr. Nation, was privately printed at the Castle Press, Pasadena, Calif.

WILLIAM B. BEAN, M.D.

A History of the American College of Chest Physicians. By J. Arthur Myers, M.D., F.C.C.P. Price, not given. Pp. 135, with 58 pages of illustrations. Buynes Printing Co., El Paso, Texas, 1959.

For the silver anniversary, the twenty-fifth birthday, of the American College of Chest Physicians, Dr. Myers has prepared a thorough sketch of the history of this increasingly important organization, whose journal, *Diseases of the Chest*, has long since outgrown its original focus on the problems of tuberculosis. The American College of Chest Physicians has now become international. Its increasing scope is particularly important when the range of chest diseases has broadened under the impact of chemotherapy and surgery.

Few people are aware of how profoundly important in the success of medical societies is the permanent staff. It keeps the organization going during the large part of the year when the society is not in session. This has been true notably of Murray Kornfeld, who has been the vital influence in the growth of the American College of Chest Physicians. The achievement of Mr. Edward Loveland in advancing the work of the American College of Physicians is comparable.

The format of the book is interesting. There are many illustrations. The brownish-mauve color of the pictures, which sounds awful, is unobtrusive. This document will interest those who wish to know something of the organization and function of a contemporary medical society.

WILLIAM B. BEAN, M.D.

The Manifold and The One. By Agnes Arber. Price, 18 shillings. Pp. 146, with no illustrations. John Murray Publishers, Ltd., 50 Albemarle St., London, W. 1, 1957.

Anyone who has been charmed with Agnes Arber's book of philosophy for biologists and other scientists, "The Mind and The Eye," will be curious to know something of her completely different work, "The Manifold and The One." In the brief compass of less than one hundred fifty pages, she has made courageous efforts to overcome the limitations of language in describing her searches into the depths of philosophy and religion for an understanding of the significance of life. The influence of Chinese philosophy and Zen Buddhism as well as the classical philosophers of the West permeate the pages. Unless one is willing to spend many hours pondering the significance of very complicated problems, he will not benefit by studying this provocative book. This essay illustrates the perplexity of trying to think about the one and the many with the simple linear thought and argument which suffices for scientific study and exposition. In a contest which has defied all prophets, seers, and religious people, the effort is still a defeat, but one that is heroic. If only a few understand

it, it will have been worth while calling it to the notice of physicians whose interests are not confined to practical matters.

WILLIAM B. BEAN, M.D.

Science and Education at the Crossroads: A View from the Laboratory. By Joseph W. Still, M.D.; Introduction by Malvina Lindsay. Price, $3.75. Pp. 140, with no illustrations. Public Affairs Press, 419 New Jersey Ave., S. E., Washington 3, D. C., 1958.

There is no rest from reminders that we are at a nodal point in the history of man and of science. Dr. Still's background in laboratory investigation, as well as his military experience and his work in public health and in general practice, give him a high vantage point from which to look at the present position and hopes of science and education. His view is that science indeed has had some responsibility for producing the great problems of the modern age and, therefore, has an obligation to help in the solutions of these problems. An effort is made throughout to apply scientific study to global problems, the complexity of which keeps the book from being anything more than an outline of general principles. The first part of the book deals with short-range problems, and the second considers the longer view. Anyone who is aware of how little personal experience the average politician and, indeed, statesman of our time has in science will agree that most of the suggestions in this book are appropriate. Not that science should settle every issue, but there are concepts which can be understood only by people who are familiar with science from the inside as well as from the outside. This is especially necessary in the highest places of government. Our leaders have not avoided two catastrophic wars within three decades.

The writer proposes getting scientific advisers to help politicians make closer study of the organization and collection of information, as well as its storage and distribution in scientific communication and general education. The notion of recruitment of youth for science and reminders of the eternal struggle necessary to retain even a modicum of freedom among scientists and academic people are very stimulating. Of course, it is necessary for much of the book to be oversimplified. The author recognizes throughout that he is dealing with not only complex but happily controversial subjects.

An annoying stylistic quirk is the excessive use of quotations, italics, and dashes, giving the reader the feeling that the writer had to rely on extra stimuli to keep the attention of the reader. In a book of this kind it is awkward to single out a few contemporary people for praise as he has done, since the book is not a general scrutiny of the contribution of scientists and educators to our progress. On the whole, despite the fact that one may not agree with everything he says, this is a very stimulating book and should be in the hands not only of scientists and educators, but politicians and statesmen as well.

WILLIAM B. BEAN, M.D.

Circulation: Proceedings of the Harvey Tercentenary Congress. By John McMichael, M.D., F.R.C.P., F.R.S. Price, not given. Pp. 503, with 200 illustrations. Charles C Thomas, Publisher, 307-327 E. Lawrence Ave., Springfield, Ill., 1958.

Celebrations of the tercentenary of the death of Harvey have taken many forms. The publication of translations of his books, many meetings, celebrations, and orations mark the occasion for rendering tribute to one of the true heroes of medicine. As is to be expected of a great man about whose genius three hundred annual orations have already drained the field dry, not much new was said. Rather, the present state of cardiovascular knowledge and investigation has been the theme of much of the homage to Harvey. So it is with this book. It is an up-to-date synopsis of work being done over much of the broadening territory of cardiovascular physiology and disease. The Harvey Tercentenary Congress provided the auspices for the transactions which are published in this handsomely prepared volume, brought out under the editorship of John McMichael. Ranging from historical details to the most recent scientific advances in research and therapy of the heart and circulation, we have a panorama of what may be looked upon as the natural development of Harvey's discovery—really, his invention—of the experimental method and its fortunate subject, the circulation of the blood. It is especially notable that some of the ceremonies of this congress consisted of the transatlantic joining of hands of many English speaking peoples, investigators in England and America, to pay filial tribute to a great man. His greatness fluorishes and does not fade as the years go by. The volume is worthy of Harvey, founder of modern physiology and clinical science.

WILLIAM B. BEAN, M.D.

The Clinical Physiology of Physical Fitness and Rehabilitation. By Ernst Jokl, M.D. Price, $8.50. Pp. 194, with 85 illustrations. Charles C Thomas, Publisher, 307-327 E. Lawrence Ave., Springfield, Ill., 1958.

The athletic superiority of Americans is now pretty much a myth, with Russia beginning to dominate the Olympics, even producing basketball teams and invading the gentlemanly sport of tennis. Not only military people, coaches, and those who devote their life to "physical education," but an increasingly obese leisure class has come to express an interest in physical fitness. This interest generally fades away when it is suggested that exercise might be something which they should indulge in personally. During World War II, great advances were made in systematic studies of performance. The concept of hypothetical "fitness" or "physical fitness" was dignified with the element of authority and scientific exactitude, and many fitness tests were developed. The outcome of all the fuss was that, while physical performance of any kind requires physique, a physiochemical readiness to make various motions, innate skill, and the additional facility which training brings, no sure method was ever devised to test motivation. It could only be said that, having accomplished so many motions, the cost to the subject measured in physiological terms bore a certain relation to average experience. Ernst Jokl, who has had a distinguished career on three continents, has presented his reflections and many of his ideas in this most interesting book dedicated to Sir Charles Sherrington. The book is fascinatingly different from the usual textbook. It incorporates the Buckston Browne Essay, awarded by the Harveian Society of London. The book contains many reproductions of the title pages of classical textbooks, photographs of Olympic champions and others who have performed great feats of physical prowess despite all kinds of physical limitations, and other clinical and x-ray data. The connection of many of the items with physical fitness is remote in the strict sense, though hardly any problem in health or disease does not have some bearing on it. The numerous allusions to sudden death are not to be found in the somewhat abbreviated index. The extensive opportunities for reconditioning and rehabilitation are brought out in interesting detail. There are a few minor misprints, such as fits of consciousness rather than fits of unconsciousness. The theme of this book might be called "The Wisdom of the Body," Starling's striking phrase. It is an exemplification of how far training, exercise, and hygienic living can go toward preventing disease or compensating for disease by rehabilitation. This is a scholarly and delightful book with a real personal flavor. It will be of great interest to those who continue to use their muscles. It may produce some nostalgic twinges in those who only use their muscles to hold their head at half mast as they slump in their seats.

WILLIAM B. BEAN, M.D.

Clinical Evaluation of New Drugs. By S. O. Waife, M.D., and A. P. Shapiro, M.D. Price, $7.50. Pp. 223, with no illustrations. Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 49 E. 33d St., New York 16, 1959.

Ten to twenty years ago, if a novice wished to undertake an experiment or thought of a career in medical research his first move would be to get advice from someone who was actively engaged in such work. Apprenticeship was the initial step in this career. Little biographical material was available to indicate what might have been the motivating force of persons whose careers in clinical investigation were successful. There was no collection of advice or instructions. The do-it-yourself, trial-and-error system or lack of system prevailed, but now, in teaching, residency, and research, the rules are growing formal. One fixed route is followed by most, and here is a book which is a Baedeker for the beginner.

In this new book devoted to many of the complex aspects of the clinical evaluation of new drugs, Waife and Shapiro have collected sixteen essays on the principles and practice of evaluating new drugs. The essays range over such diverse aspects of the problem as the nature of pharmacologic and pharmacodynamic problems; animal experimentation as a necessary preliminary to human studies; the experimental design, employment of statistics, subjective responses, and the role of placebos in their evaluation; the ethics of experimentation in human beings; the investigator, his training, background, and objectives. The second part of the book deals with special problems of investigating new drugs in different kinds of clinical disorders and in normal persons. There is some unevenness in the several chapters, though each essay has been prepared and edited with care. The contributors represent a good cross section of those interested in clinical research, including clinicians, teachers, laboratory investigators, and representatives of the pharmaceutical industry. The intricate interrelations

of various aspects of research, drug manufacturers, clinical trials, and therapeutic effectiveness are illustrated from many different angles. The advances of the recent past have occurred because the spirit of research inspired dedicated investigators. Our present stage of medical practice has advanced a long distance in recent years with the application of scientific principles to therapy in medical practice. We have now a host of specifics, where in the past very few were available.

Physicians and clinical investigators will find much of practical importance as well as of theoretical interest. But many arms of government, research foundations, universities, and medical colleges will find much pertinent material. Among the numerous federal agencies which have a vital interest in matters set forth in this book are Food and Drug Administration, The U. S. Public Health Service, and the various elements of the National Institutes of Health, The Army Medical Research Board, Chemical Corp, Armed Forces Institute of Pathology, Office of Naval Research, Naval Medical Research Institute, Aeromedical Laboratory, Medical Nutrition Laboratory, Veterans Administration, The Department of Agriculture, National Science Foundation, National Research Council, National Academy of Science, and other government bureaus. This is in addition to all the universities and medical schools, and some with many departments carrying on research, foundations, such as the Rockefeller, Macy, Markle, Millbank, and Commonwealth, large clinics and voluntary health organizations, and, of course, the drug industry.

WILLIAM B. BEAN, M.D.

The Rewards of Medicine and Other Essays. By Hugh Barber. Price, 15 shillings net, in Great Britain. Pp. 140, with no illustrations. H. K. Lewis & Co., Ltd., 136 Gower St., London, W. C. 1, 1959.

Sage and mellow reflections of a person who has spent a lifetime in the practice of medicine make interesting or dull reading, according to the experience and the ability of the person to convey his ideas. This collection of essays, mostly published in *Guy's Hospital Gazette* or the *Practitioner*, range from a discussion of Smollett's contribution to medicine to the act of dying. There is a general discussion of old age, entitled "Old Father William's Fancies," which contains more wisdom than many of the writings of those who, somewhat ostentatiously, call themselves geriatricians or gerontologists. Permeating these pleasantly casual and offhand talks is a clear vision of English history and English literature which gives flavor to the many morsels of miscellaneous information. This book illustrates in a most delightful way the rewards of medicine as they are seen through the eyes of a physician of the "old school." It has charm, dignity, and grace, as well as a store of fascinating information about British medicine and people. An interesting commentary on Barber's essay on Erasmus Darwin is found in his quotation, "Sir William Osler once said that in the scientific world the credit does not go to the man who first had the idea but to him who convinced the world." This idea, which may have originated hundreds of years ago, is actually almost an exact quotation of a comment of Francis Darwin, the great, grandson of Erasmus. Francis Darwin's father, Charles, had this to say about credit and fame in scientific matters: "Within late years several reviewers have given credit to Fritz Mueller and Hackel who undoubtedly have worked it out much more fully and in some respects more correctly than I did. I had materials for a whole chapter on the subject and I ought to have made the discussion longer; for it is clear that I failed to impress my readers; but he who succeeds in doing so deserves in my opinion all the credit." The book is full of wisdom and ideas which set the train of association in motion. Such pleasant stimulus is always worth getting.

WILLIAM B. BEAN, M.D.

An Autumn Gleaning: Occasional Lectures and Addresses. By H. H. Dale, O.M., G.B.E., F.R.S., M.D., F.R.C.P. Price, not given. Pp. 225, with no illustrations. Interscience Publishers, Inc., 250 5th Ave., New York 1; Pergamon Press, Inc., 4 & 5 Fitzroy Sq., London, W. 1, 1954.

An irresistible urge to collect a volume of essays or write an autobiography often assails those who have precious little to say but have an enhanced notion of their own uniqueness. Only rarely do such perceptive scholars as Sir Henry Dale, who have made significant contributions to science and have achieved wisdom which makes their words valuable to society, set them before us. In this respect, Sir Henry Dale reminds one of Sherrington in the scholarly pursuit of scientific quests carried to successful fulfillment and the ability to put them down in delightful prose. In this miscellaneous collection of essays and speeches,

produced over a span of approximately twenty years, he has brought together what he chooses to call "An Autumn Gleaning" of lectures and addresses. From a great number, he has chosen to include not so much his scientific investigations as those illustrating the spirit of the times, especially the impact of science on society during his life. To anyone interested in medical education, his essays on science in education, on accident and opportunism, and on medical research as an aim in life give a scholar's insights into the close connection between science and humanism, and the no longer startling suggestion that the cultivation of science itself is an excellent method of obtaining broad culture in learning. While Dale's responsible position during World War II gave many of his talks a certain urgency born of the current military situation, this same feeling of uncertainty and urgency is one of the prevailing moods of our time, but running through his essays is the quieter stream of mellow scholarship arising from critical thinking. The fascinating story of the somewhat casual experimentation which Dr. George Oliver did on his own son leading to the discovery of Adrenalin is included, and many other interesting and charming episodes are scattered throughout the book. Only occasionally does one differ with Dale and his reconstructions of history. Certainly, the differentiation of various diseases characterized by anemia and adrenal gland disease was not perfectly clear in Addison's mind. Also, there were no new experimental tools available for William Harvey that were not available to Aristotle. Both had the scalpel, the needle, and the ligature. It was, therefore, not in any sense a technological revolution, but an intellectual one which enabled Harvey, in one massive feat, to establish the experimental method of interrogating nature while demonstrating the circulation of blood. But these are tiny flaws in this happy gleaning of autumn leaves from a noble tree. They are still worth careful reading and should be browsed again and again.

WILLIAM B. BEAN, M.D.

A Short History of Anatomy and Physiology from the Greeks to Harvey. By Charles Singer. Price, $1.75. Pp. 209, with 20 illustrations. Dover Publications, Inc., 920 Broadway, New York 10, 1958.

In the field of publishing medical books, expense has always been a considerable and sometimes a sore impediment to the undergraduate student or the young man who wished to collect books. Until recently, no one has gotten out a series of well printed and designed paper-back editions. Now the Dover Publications, Inc., in New York, is reissuing a number of medical classics. They have brought out Charles Singer's volume, long out of print and a collectors' item. The beginnings of anatomy and physiology are traced from their very earliest stages, when medicine in so many ways was a crude hodgepodge of fear and mythology. Our fascination with the current fabulous advances in laboratory science makes us forget that the modern development of medicine depended first of all upon recognition of the human body, understanding of its anatomy, and willingness to confront biological reality in man. Though this seems a truism, for long ages dissection of the human body never occurred to anyone. Later, it was either forbidden completely by religious doctrines and dogmas or was permitted only under the most inauspicious circumstances, such as making dissections on criminals who were to be tortured or put to death. Tradition so sterilized the inquisitive mind of man during a large period of Western history that the writings of early Greeks and Romans were taken as doctrine, even though much of their anatomy was derived from work on primates, dogs, pigs, and other lower animals. So obsessed was mankind with the virtues of antiquity that Galen was trusted rather than the witness to the truth which the senses provided. The tremendous impact of the men of the Renaissance led great anatomists to a peak in Vesalius, whose magnificant dissections and Calcar's beautiful and artistic plates brought anatomy almost at one instant out of the range of mythology into the arena of reality. The entire story of this development and the men who contributed to its various phases are set forth in this delightful volume, which is now cheap enough to be in the hands of any medical student of whatever age. Those who read it will be rewarded by a clearer insight into the anatomical basis of physiology—the difficult and laborious steps by which structure and function came to be understood as reciprocally related among the sciences which form the basis of medicine. Perhaps because of the effect of the numerous drawings and plates in the book, anatomy rather than physiology gets a major proportion of the emphasis. This also reflects the actual emphasis on anatomy rather than physiology in its early days.

WILLIAM B. BEAN, M.D.

Greek and Latin in Scientific Terminology. By Prof. Oscar E. Nybakken. Price, $5.95. Pp. 321, with no illustrations. Iowa State College Press, Press Building, Ames, Iowa, 1959.

Prof. Nybakken, chairman of the Department of Classics of the State University of Iowa, for many years has taught a class in scientific Latin and Greek, giving prospective medical and professional students an opportunity to learn in a relatively painless but none-the-less effective way the rudiments of word origins and of word formation. This excellent book, "Greek and Latin in Scientific Terminology," while it is not designed specifically for medical students or physicians, contains all the information necessary for a person who wishes to explore the mysteries of scientific nomenclature and learn the ground rules under which the words have developed. For instance, few of us realize that the position of the accent on the word *thymos* can make it mean either a warty excrescence or the soul.

Any physician or scientist interested in words and writing will welcome a book that even the novice may use as a primer in studying word derivation and the meaning of words. The search for the precise word and exact shade of meaning forms the theme of this book. The excuse for any scientific nomenclature is its power to express precisely very complex ideas.

For more than a century, the decline in study of the classics has characterized formal education in this country. Despite whatever one may think about a study of the classics as a rational discipline with real virtue in education, one can scarcely comprehend medical science and medical writing without a knowledge of Greek and Latin. This can be acquired by memorizing definitions or by study of the languages which have served as building blocks for new words.

This book can be used as a reference book or for light reading for those who like to browse in dictionaries. It explains not only where scientific words come from but also the procedures by which they should be constructed. The question of how to use language in manufacturing new words has been a thorny one. The dissemination of knowledge of definitions has hardly kept up with the demands placed on both novice and expert. The number of technical words in medicine literally runs to seven figures. This mass of words is necessary to express scientific ideas precisely. New ones are added almost daily. As if this were not bad enough, a tremendous number of neologisms come from the imaginative but bemused constructor of trade names for drugs and equipment. We condone sloppy writing, improper use, and mispronunciation of technical terms and fail to maintain standards against medical and scientific illiteracy.

There is a most seductive tendency for physicians to use long words where short words are needed. Our interns and residents fall into an almost unintelligible lingo of abbreviations, misconstructions, and downright error, uncorrected and often actually encouraged by the bad example of their teachers. It has been hard to find good guides for those who wish to increase their understanding of words and their proper employment of the technical language of medicine.

Each branch of science develops its own jargon. Among the social sciences, so-called, there is an almost grotesque flair in the use of sterotyped words, sometimes to express absolutely no meaning at all.

The strange terror of Latin and Greek for those who have not studied them should be dispelled by this book, which is as easy to use as a reference and is designed to be employed as a textbook.

Nybakken, discussing economy in the use of new word formations, says: "Words which are unduly long or which almost defy pronunciation should not be used unless absolutely necessary. Terms like 'Brachyuropushkydermatogammarus,' 'pneumoultramicroscopicsilicovolcanokoniosis,' and 'Hepaticocholangiocholecystenterostomy' offend good taste." A term like "laryngotracheobronchitis," however, may be justified in spite of its length because it describes so exactly the areas of inflammation and because its pronunciation is not excessively difficult. It may interest the purists who are upset by combinations of Latin and Greek, such as the word appendicitis, that Nybakken takes a liberal view of such polyglots and conglomerates, and this seems particularly reasonable in view of the tremendous incorporation of Greek in the structure of the Latin language itself.

This excellent book should help anyone whose demon of writing drives him to the construction of a new word if he follows the rules and the spirit set forth in this very helpful treatise, which might gull some of the bemused neologists who scar the literary terrain with wounds of linguistic ineptitude.

WILLIAM B. BEAN, M.D.

News and Comment

ANNOUNCEMENTS

Meeting of American Psychosomatic Society.—The American Psychosomatic Society will hold its Seventeenth Annual Meeting at the Sheraton-Mount Royal Hotel, in Montreal, on Saturday and Sunday, March 26 and 27, 1960.

The program committee would like to receive titles and abstracts of papers for consideration for the program no later than Dec. 1, 1959. The time allotted for presentation of each paper will be 10 or 20 minutes.

Abstracts, of two or three pages, in nine copies, should be submitted for the program committee's consideration, to the Chairman, Eric D. Wittkower, M.D., at 265 Nassau Rd., Roosevelt, N. Y.

Symposium on "Salt and Water Metabolism."—"Salt and Water Metabolism" will be the subject of a two-day symposium to be held by the New York Heart Association, at the Hotel Biltmore, on Dec. 11-12. Alfred P. Fishman, M.D., chairman of the association's Scientific Sessions Committee, is in charge of the program, and 23 speakers will take up all phases of the subject.

The morning session on the first day, under the chairmanship of Homer W. Smith, Sc.D., will consider the "Theory of Solutions"; Richard J. Podolsky, Ph.D., will discuss the "Structure of Water and Electrolyte Solutions"; Irving M. Klotz, Ph.D., "Protein Solutions," and Alexander Mauro, Ph.D., "Semipermeable Membranes."

Robert F. Pitts, M.D., of Cornell University, will be chairman of the afternoon session on that day, devoted to "Intrarenal Sites of Salt and Water Exchange." Topics to be covered will be "Osmotic Concentration and Dilution in the Mammalian Nephron," by Carl Gottschalk, M.D.; "Reabsorption of Sodium and Chloride Ions by the Amphibian and Mammalian Nephron," by Gerhard Giebisch, M.D.; "Ion Exchange Mechanisms in the Nephron," by Robert W. Berliner, M.D., and "Stop-Flow Studies on Ion and Water Reabsorption in the Nephron of the Dog," by Richard L. Malvin, Ph.D. and Water S. Wilde, Ph.D.

An after-dinner address that evening will be given by George Wald, Ph.D., of Harvard University, on "Salt, Water and Vertebrate Metamorphosis."

The second day will open with a session on "Extrarenal Salt and Water Metabolism," presided over by John V. Taggart, M.D., of Columbia University. "Connective Tissue" will be the subject of a paper by Saul J. Farber, M.D.; "Ion Transport in the Gut," by Alfred Gilman, Ph.D.; the "Salt Gland of Marine Birds," by Knut Schmidt-Nielsen, Ph.D.; "Ion Movements in the Eye," by V. Everett Kinsey, M.D., and "Electrolyte Excretion in Bile," by Henry O. Wheeler Jr., M.D.

The closing session will be devoted to "Extrarenal Regulation of Salt and Water Exchange," with George Sayers, Ph.D., of Western Reserve University, as chairman. Gordon L. Farrell, M.D., will speak on "Glomerulotropin"; Louis Welt, M.D., on "Volume Receptors"; Wilbur A. Sawyer, M.D., on "Antidiuretic Hormone"; James G. Hilton, M.D., on "Adrenocorticotrophic Action of Antidiuretic Hormone," and Fred C. Bartter, M.D., on "Aldosterone."

Application for registration should be made to A. P. Fishman, M.D., c/o New York Heart Association, 10 Columbus Circle, New York 19. No fee is involved.

GENERAL NEWS

Medical Books for Poland.—The Polish Institute of Arts and Sciences in America has issued a call to all American medical groups, colleges, hospitals, and physicians to contribute new and used medical textbooks, reference books, and journals to medical schools and teaching hospitals. In the plea for contributions of medical books and reference books the chairman of the project, Mr. Maryan Chodacki said, "The effects of the devastations of war upon medical education in Poland are far from overcome even though the fighting in Poland ended fifteen years ago. There are many physicians and medical students in Poland who read English and who are avid for American medical books and journals. Following the long traditions of American Medicine which has assisted so many other war devastated nations in

rebuilding their medical education programs, American physicians, medical groups, colleges and hospitals can now send their contributions through the Polish Institute of Arts and Sciences in America. This organization is prepared to act as a receiving center for such contributions and to pay all shipping costs."

Individual persons and organizations may send books and journals prepaid postage, express or freight, to Mr. Maryan Chodacki, Polish Institute of Arts and Sciences in America, 145 E. 53d St., New York 22. Persons and groups with contributions but without funds to pay shipping costs to New York should write to Mr. Chodacki.

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(1) Rubin, A., and Babbott, D.: J.A.M.A. *168*:498, (Oct. 4) 1958. (2) Kinsey, A. C.; Pomeroy, W. B., and Martin, C. E.: Sexual Behavior in the Human Male, Philadelphia, W. B. Saunders Company, 1948.

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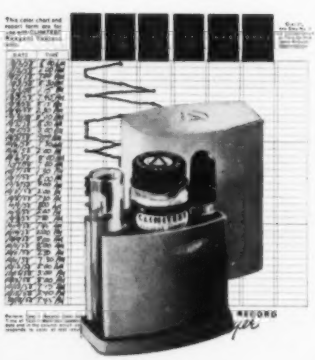

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CHEMISTRY OF PANCREATIC DISEASES *by* **Harris Busch,** *Associate Professor of Pharmacology, University of Illinois College of Medicine.* Doctor Busch unravels with great chemical clarity the deviations in the external secretion of pancreatic juice and its enzymes that lead to systemic disorders in spite of the reserve of pancreatic acini. *Publication date November 1959*

RADIATION INJURY IN MAN: Its Chemical and Biological Basis, Pathogenesis and Therapy *by* **Eugene P. Cronkite,** *Head, Division of Experimental Pathology, and* **Victor P. Bond,** *Head, Division of Microbiology; both of Medical Research Center, Brookhaven National Laboratory, Upton, New York.* What is the level of permissible occupational exposure to radiation? What is the level to be used therapeutically in cancer? What are the ultimate genetic effects on mankind? These and hundreds of other questions are answered in this momentous work. *Publication date November 1959*

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THE CHEMISTRY OF LIPIDS IN HEALTH AND DISEASE: A Review of Our Present Knowledge of Lipids; Their Chemical Structure; Their Breakdown and Synthesis in Living Organisms; Their Place in Human Nutrition; and Their Abnormalities of Metabolism in Disease *by* **H. K. King,** *Senior Lecturer in Biochemistry, The University of Liverpool. Publication date November 1959*

BIOCHEMISTRY OF BLOOD IN HEALTH AND DISEASE *by* **I. Newton Kugelmass.** Coverage ranges from the unique properties of circulating blood which enable its diverse functions throughout the body, to the gamut of its dynamic activities in transporting all components, regulating tissue processes and defending organ integrity. Lucid interpretations of blood changes in health and disease provide accurate chemical diagnosis in the cause of more effective clinical therapy. *Publication date August 1959*

NEUROCHEMISTRY OF EPILEPSY: Seizure Mechanisms and Their Management *by* **Donald B. Tower,** *Chief, Section of Clinical Neurochemistry, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland.* Doctor Tower transforms anticonvulsant therapy from empirical to rational procedures. How the newer compounds act directly upon abnormally-firing neurons to correct their metabolism and stabilize their cellular environment. *Publication date November 1959*

CHEMICAL MICROMETHODS IN CLINICAL MEDICINE *by* **R. H. Wilkinson,** *Assistant Chemical Pathologist, The Hospital for Sick Children, London.* With remarkable simplicity the author has developed his micromethods for office and hospital practice whether the immediate problem is diagnosis and treatment of acute or chronic signs of malnutrition or disease. *Publication date September 1959*

THE CHEMISTRY OF HEREDITY *by* **Stephen Zamenhof,** *Associate Professor of Biochemistry, Columbia University College of Physicians and Surgeons.* Everyone has been looking for a "popular explanation of the chemical basis of heredity." HERE IT IS. Explains the fundamentals without wearing recourse to the difficult maze of organic chemistry, yet without sacrificing the accuracy of the reported findings and conclusions. *Publication date July 1959*

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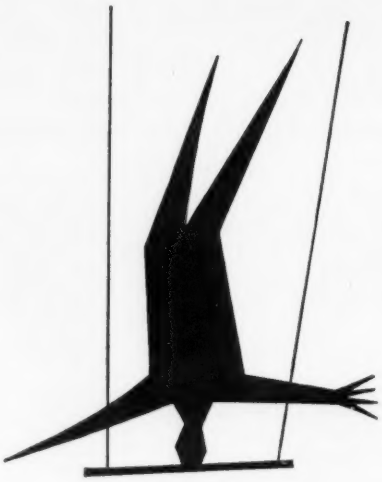
moderate low-fat and well-balanced food values in cereal and milk serving



Among breakfast main dishes, the cereal and milk serving merits consideration when a reduction of dietary fat is indicated because *it ranks low in fat and provides well-balanced food values.* Few foods at such small cost can better its moderate low-fat, well-balanced nutritional contribution as shown in the table below. Served with nonfat milk, the fat content is very low.*

nutritive composition of average cereal serving

	Cereal, 1 oz. Whole Milk, 4 oz. Sugar, 1 teaspoon	Cereal** 1 oz.	Whole Milk 4 oz.	Sugar 1 teaspoon
CALORIES	203	104	83	16
PROTEIN	7.3 gm.	3.1 gm.	4.2 gm.	
FAT	5.3 gm.	0.6 gm.	4.7 gm.*	
CARBOHYDRATE	32.2 gm.	22 gm.	6.0 gm.	4.2 gm.
CALCIUM	0.169 gm.	0.025 gm.	0.144 gm.	
IRON	1.5 mg.	1.4 mg.	0.1 mg.	
VITAMIN A	195 I. U.	—	195 I. U.	
THIAMINE	0.16 mg.	0.12 mg.	0.04 mg.	
RIBOFLAVIN	0.25 mg.	0.04 mg.	0.21 mg.	
NIACIN	1.4 mg.	1.3 mg.	0.1 mg.	
ASCORBIC ACID	1.5 mg.	—	1.5 mg.	
CHOLESTEROL	16.4 mg.	0	16.4 mg.*	

*Nonfat (skim) milk, 4 oz., reduces the Fat value to 0.1 gm. and the Cholesterol value to 0.35 mg.
**Based on composite average of breakfast cereals on dry weight basis.

Cereal Institute, Inc.: Breakfast Source Book. Chicago: Cereal Institute, Inc., 1959.

Hayes, O. B., and Rose, G. K.: Supplementary Food Composition Table. J. Am. Dietet. A. 33:26, 1957.

Watt, B. K., and Merrill, A. L.: Composition of Foods-Raw, Processed, Prepared. U.S.D.A. Agriculture Handbook No. 8, 1950.

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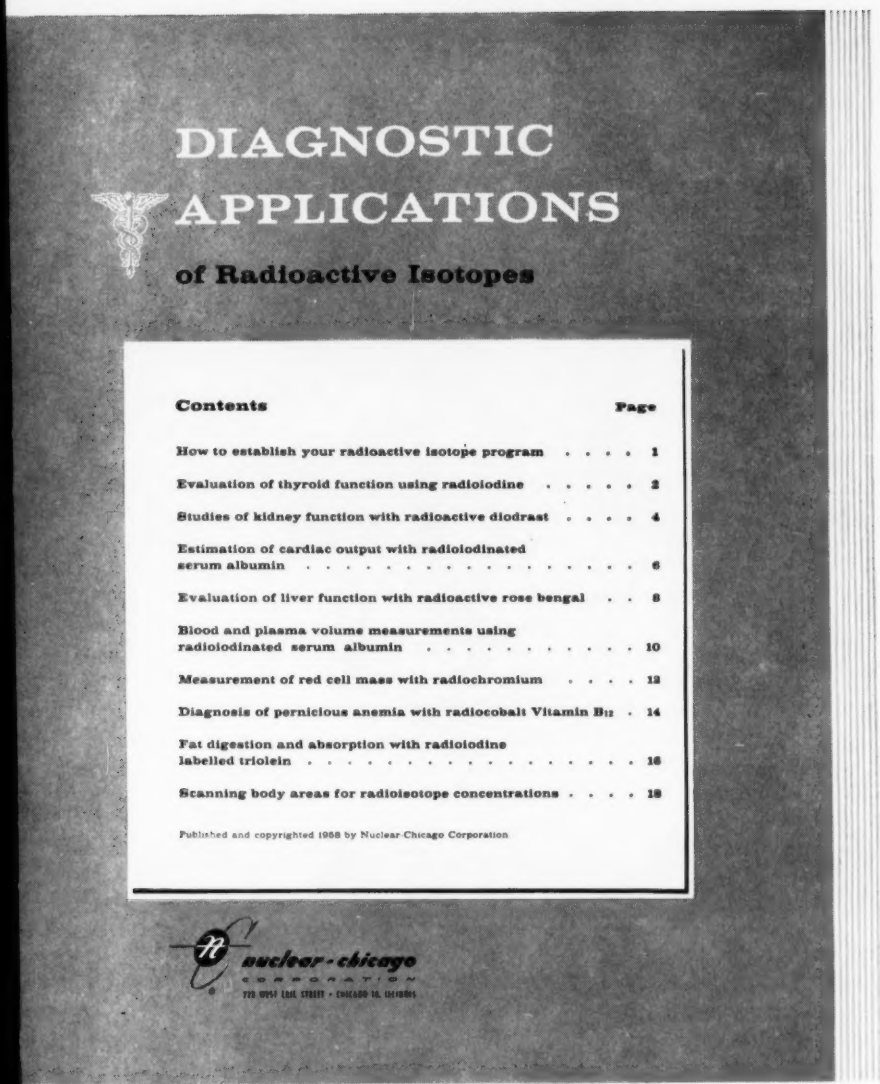
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(Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.)

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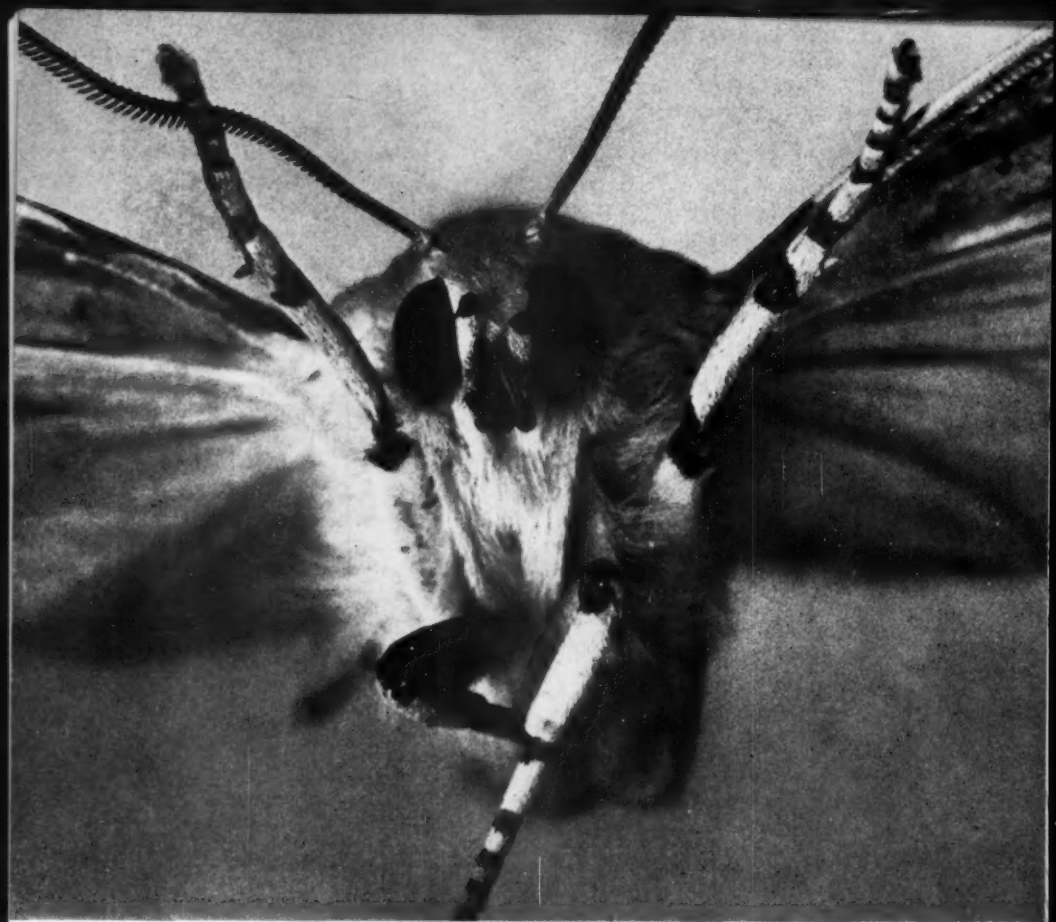

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